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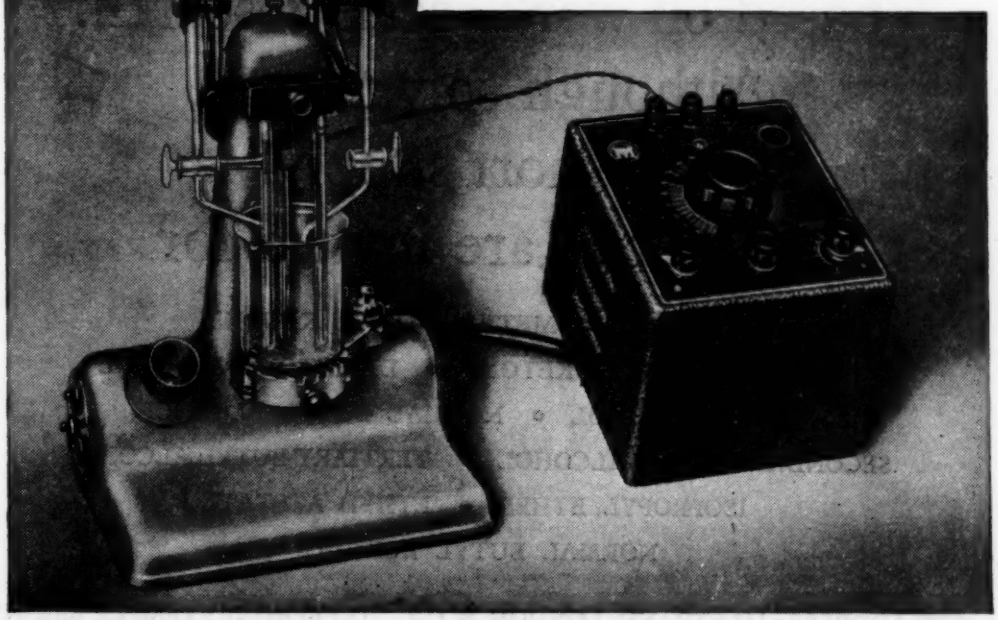

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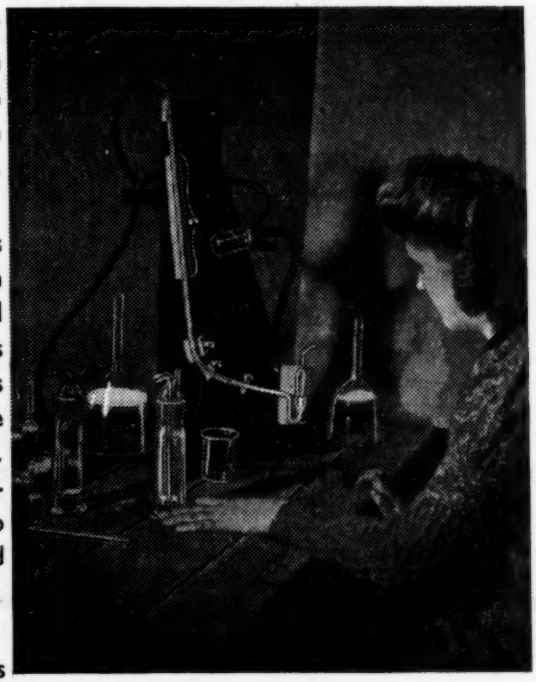

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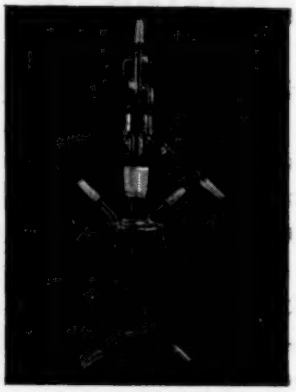

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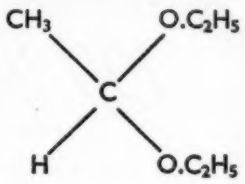


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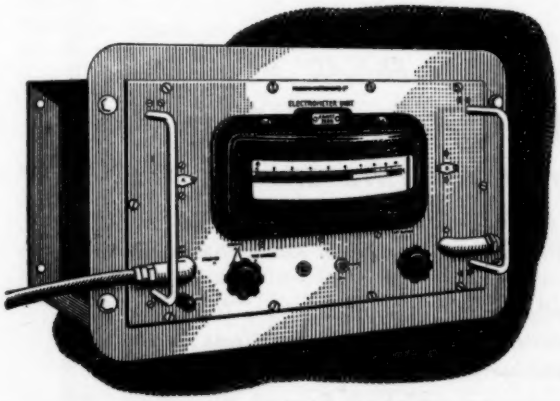

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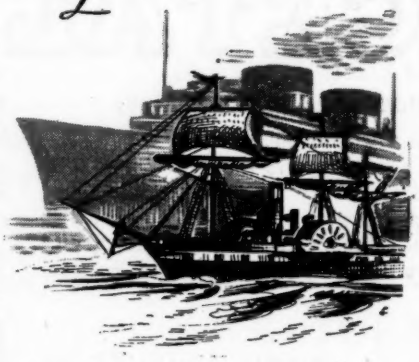

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# ERRATA.

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| Page | Line | |
|---|---|---|
| 149 | | In note (29), *for* "$C_{28}H_{24}O_{16}N_4$" *read* "$C_{28}H_{24}O_{16}N_{10}$". |
| 234 | | Table XII, line 3 within frame, last entry, *for* "$[E_g]$" *read* "$[E_g^-]$". |
| 267 | | Fig. 3 (*b*), *for* "960" *read* "969". |
| 287 | 5* | *for* "$E_g$" *read* "$E_g^-$". |
| 343 | 3 | *for* "4 : 4'-*Di*-(*ω-carbomethoxymethyl*)-*DT*" *read* "4 : 4'-*Di*-(*ω-carbomethoxymethoxy*)-*DT*". |
| 514 | 2 | *for* "Callow and Strain" *read* "Callow and Young". |
| 719 | 21 | *for* "$C_{20}H_{24}N_5Br$" *read* "$C_{26}H_{36}N_5Br$". |
| 731 | | *delete* the Cl from formula (XX), and, on the next line of text, *for* "(XXI)" *read* "(XX)". |
| 827, 829 | | In title, *for* "*Methyldi*-2-(*chloroethyl*)*amine*" *read* "*Methyldi*-(2-*chloroethyl*)*amine*". |

* From bottom.

glycol ethers, easily hydrolysable to dialkylacetaldehydes, and the preparation of phenyl ethers, incidentally proving the structure of anethole. An earlier investigation, with Auger, on the action of malonyl chloride on aromatic hydrocarbons in the presence of aluminium chloride, led to the production of β-diketones of the type, R·CO·$CH_2$·CO·R, which had " acid " properties and formed metallic derivatives; by decomposition with concentrated alkalis these β-diketones proved to be a convenient source of ketones and acids of the general types, R·CO·Me and R·$CO_2$H, respectively.

Auguste Béhal died on 2nd February, 1941, at Mennecy (S. et O.). He never doubted that France would regain her liberty and greatness.* C. S. Gibson.

* The writer is greatly indebted to MM. André Kling and M. Sommelet and to (the late) M. Damiens for information regarding certain details of Béhal's career. The photograph is taken from a commemorative medal struck at the time of Béhal's retirement.

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## 240. *Addition of Dinitrogen Tetroxide to Olefins. Part I. General Introduction.*

By Norman Levy and Charles W. Scaife.

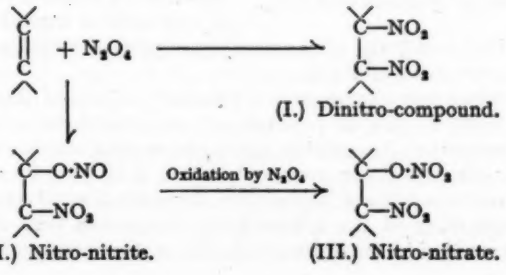
By the addition of dinitrogen tetroxide to the lower olefins in the liquid phase, dinitroparaffins, nitro-alcohols, and nitroalkyl nitrates are produced in good total yield. The first products are a dinitroparaffin and a nitro-nitrite, of which the latter is unstable and requires conversion into nitro-alcohol by reaction with water or alcohol as an essential first stage in satisfactory recovery of pure products. The nitro-nitrate is formed by oxidation of the nitro-nitrite. Difficulties previously inherent in this field have been overcome by use of pure tetroxide, conversion of the nitro-nitrite into stable nitro-alcohol, and the use of ether or ester solvents for some of the lower olefins. Ethylene itself and the higher olefins may be satisfactorily nitrated without solvent. Control of the reaction at or below room temperature is a further essential, while interference by dinitrogen trioxide may be prevented by addition of oxygen.

Only two modes of addition of the tetroxide appear, *i.e.*, as two nitro-groups or as one nitro- and one nitrite group, the latter invariably being attached to the carbon with the fewer hydrogen atoms.

The present series of papers describes research carried out on the addition of dinitrogen tetroxide ($N_2O_4$) to olefins, a systematic study of which has been made during the past six years in these laboratories. This has resulted in general methods for the preparation of dinitroparaffins, nitro-alcohols, and nitro-alkyl nitrates, applicable as far as can be seen to all olefins and affording many substances not previously reported. The literature on this subject, apart from the conflicting descriptions of products, is confused for a variety of reasons : (1) the use of impure tetroxide or " nitrous gases " consisting of mixtures of tri- and tetr-oxide and nitric and nitrous acids, (2) oxidative side reactions leading to formation and subsequent addition of the trioxide, (3) failure to note the influence of reaction medium, in certain cases decisive, on the course of reaction, and (4) difficulties in separating the products, arising in part from the instability of some of the primary products. Many products described by earlier workers are now known to be mixtures; in particular, it may be said that reasonably pure dinitro-paraffins have hitherto only been obtained from fully-substituted ethylenes, *e.g.*, tetrahaloethylenes (Biltz, *Ber.*, 1902, **35**, 1528) and tetramethylethylene (Michael and Carlson, *J. Org. Chem.*, 1940, **5**, 14). Dinitro-derivatives of simple olefins, *e.g.*, propylene, *iso*butylene, 1- and 2-butylene, have only now been satisfactorily prepared from the olefins and clearly characterised.

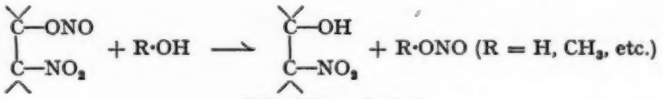
Compounds other than dinitroparaffins mentioned in the literature as arising from the reaction between nitrogen oxides and olefins include nitrosites (now generally regarded as bisnitronitroso-compounds), nitrosates, nitro-olefins in small amount, and oximes, but only in few cases have nitro-alcohols or nitroalkyl nitrates been isolated. Often the materials separated and defined have represented only a minor proportion of the reaction product, the major proportion having resisted identification because of spontaneous and vigorous decomposition during attempted isolation. In the work now described, the nitration procedure, together with the methods of separation devised, permits the isolation of the main products in amount substantially equivalent to the olefins consumed.

*Nitration Reaction.*—Ethylene and *iso*butylene were originally treated in the vapour phase with dinitrogen tetroxide at about 150°. Substantial oxidation also occurred, and the product was very difficult to separate, although a small quantity of solid 1 : 2-dinitroethane was isolated from the product from ethylene. Far better reaction control and recovery of nitro-compounds were obtained by liquid-phase methods now outlined.



With gaseous olefins reaction is normally carried out by passing the gas into tetroxide either liquid (b. p. 20·7°) or dissolved in an ether or ester solvent, the reaction being kept at or below room temperature by means of a cooling bath. Similar cooling should be employed with non-gaseous olefins which are usually brought into reaction by dropwise addition to the tetroxide or *vice versa*. Under these liquid-phase conditions, addition of tetroxide occurs both as two nitro-groups and as one nitro- and one nitrite group (see foot of p. 1093).

According to circumstances and subject to a degree of control, part of the nitro-nitrite is oxidised to nitro-nitrate. In the subsequent working up, which necessarily includes treatment of the crude oily product with water or alcohol, the unstable nitro-nitrite is converted into nitro-alcohol:

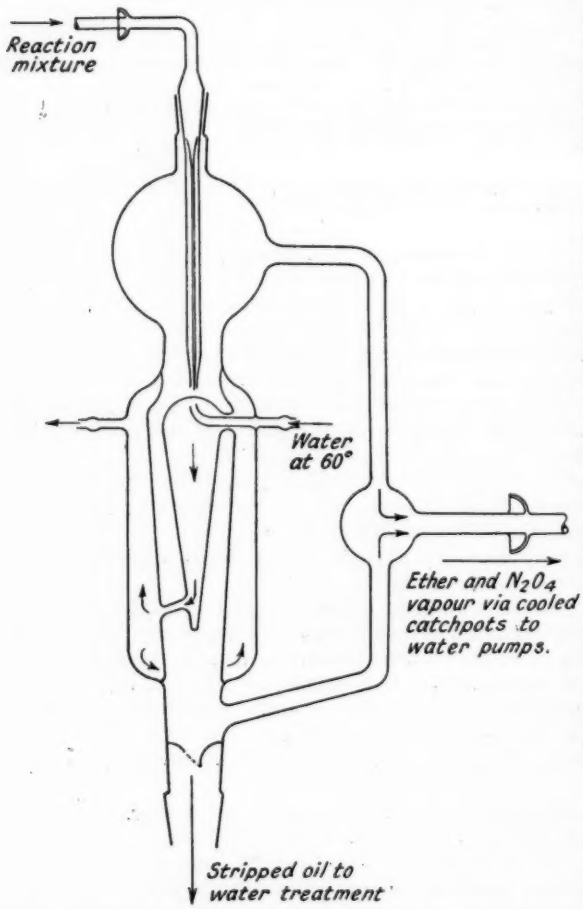



(IV.) Nitro-alcohol.

*Effect of Solvent.*—It has been found that, although ethylene and olefins such as the octylenes and *cyclo*hexene may be suitably nitrated in the absence of solvent, *i.e.*, by addition to liquid tetroxide, yet propylene and the butylenes give rise to partly oxidised substances containing little or no dinitroparaffin unless an ether- or ester-type solvent is used. Thus, passage of propylene or *iso*butylene into liquid dinitrogen tetroxide yields a product from which only the nitrate ester of the 2-hydroxy-carboxylic acid has been isolated, formed presumably from the nitro-nitrate:

$$NO_2{\cdot}O{\cdot}\overset{|}{C}{\cdot}CH_2{\cdot}NO_2 \longrightarrow NO_2{\cdot}O{\cdot}\overset{|}{C}{\cdot}CO_2H.$$

In these cases, the ether or ester solvent, *e.g.*, ethyl ether, dioxan, ethyl acetate, etc., is thought to moderate the oxidising action of dinitrogen tetroxide through molecular complex formation; with dioxan a white solid complex ($C_4H_8O_2,2NO_2$) can in fact be separated when the solvent and liquid tetroxide are mixed. Some support for this view arises from the fact that ethers with electron-attracting substituents, *i.e.*, with reduced electron availability at the oxygen atom, are unsuitable reaction media, *e.g.*, 2 : 2′-dichlorodiethyl ether and ethyl 2-nitroethyl ether. Benzyl methyl ether does, on the other hand, yield dinitroparaffins, while formic esters, *e.g.*, ethyl formate, act as intermediate types, giving rise both to dinitroparaffins, etc., and to oxidation products.




*Falling film evaporator for removal of solvent and $N_2O_4$.*

The nitration of ethylene is slow at atmospheric pressure and absorption should not be carried beyond 0·4 mol. of $C_2H_4$ per mol. of $N_2O_4$ for good yields. For propylene and the butylenes, which react rapidly, the concentration of tetroxide in the solvent is of importance, and for the higher olefins the proportion of tetroxide (molar or excess) may affect the proportions of the main products.

*Effect of Oxygen.*—A further variable is introduced through reduction of some of the tetroxide to trioxide which can give rise to undesirable or unstable side products. The introduction of oxygen into the reaction prevents or limits this tendency and yields a much more stable crude product. Addition of oxygen is not always desirable, however; in the nitration of *iso*butylene, the proportion of nitro-nitrate is increased by oxygen addition and the separation of 1 : 2-dinitro-*iso*butane by crystallisation made more difficult.

*Separation of Products.*—After completion of the reaction, excess of dinitrogen tetroxide and solvent, if used, are taken off as vapour under reduced pressure and condensed for re-use. Care must be taken in the final stage of solvent removal since the nitro-nitrites appear to be least stable when free from solvent or tetroxide. This is especially important with the lower members, where it is best to remove solvent and tetroxide by evaporation at water-pump vacuum from a falling film, allowing the solvent-free product to drip into water or alcohol for immediate conversion of the nitro-nitrite component into nitro-alcohol. A convenient and simple form of evaporator is provided in the ordinary double-surface condenser by passing warm water through

the jacket. An improved type with a conical inner element is shown in the figure (see also British Patent Application No. 17,160/45).

The crude product now consists mainly of a mixture of dinitroparaffin, nitro-alcohol, and nitroalkyl nitrate. Ethylene, propylene, the butylenes, and *cyclo*hexene give rise to nitro-alcohols soluble in water, whereas the dinitroparaffins and nitro-nitrates are insoluble. Thus, for these olefins, the nitro-alcohols are removed by water washing and later extracted with an organic solvent or fractionally distilled. The water-insoluble oil, after drying, is fractionally distilled to separate the dinitroparaffin and nitro-nitrate. Variations of this procedure are desirable with particular olefins. For instance, 1 : 2-dinitro*iso*butane is best recovered by freezing a methanol solution of the water-insoluble oil. Similarly, 1 : 2-dinitroethane is crystallised from the methanol solution of the three main products, but subsequent separation of the remaining mixture of nitroethanol and nitroethyl nitrate is made by extraction with a benzene–water mixture, the nitroethyl nitrate passing into the benzene and the nitroethanol into the aqueous layer. Further, the trimethylpentenes give rise to nitro-alcohols insoluble in water, and here the mixed product must be separated by fractional distillation. All distillations in this series must be conducted with care behind non-shatter screens, and means of rapid cooling, *e.g.*, a solid carbon dioxide–methanol bath, used if gas evolution becomes visible.

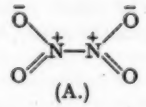
*Nitration Products.*—The main products of nitration of the olefins mentioned are tabulated below. Total yields on olefin vary between 65% and 85% of pure isolated products. In the absence of oxygen the amount

| Olefin. | Dinitrohydrocarbon. | Nitro-alcohol. | Nitroalkyl nitrate. |
|---|---|---|---|
| Ethylene | 1 : 2-Dinitroethane | 2-Nitroethanol | 2-Nitroethyl nitrate |
| Propylene | 1 : 2-Dinitropropane | 1-Nitropropan-2-ol | β-Nitro*iso*propyl nitrate |
| *iso*Butylene | 1 : 2-Dinitro*iso*butane | Nitro-*tert.*-butanol | Nitro-*tert.*-butyl nitrate |
| 1-Butylene | 1 : 2-Dinitro-*n*-butane | 1-Nitrobutan-2-ol | — |
| 2-Butylene | 2 : 3-Dinitro-*n*-butane | 2-Nitrobutan-3-ol | — |
| 2 : 4 : 4-Trimethylpent-1-ene | 1 : 2-Dinitro-2 : 4 : 4-trimethylpentane | 1-Nitro-2 : 4 : 4-trimethylpentan-2-ol | — |
| 2 : 4 : 4-Trimethylpent-2-ene | 2 : 3-Dinitro-2 : 4 : 4-trimethylpentane | 3-Nitro-2 : 4 : 4-trimethylpentan-2-ol | — |
| *cyclo*Hexene | 1 : 2-Dinitro*cyclo*hexane | 2-Nitro*cyclo*hexanol | 2-Nitro*cyclo*hexyl nitrate |

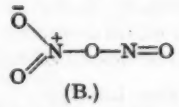
of dinitro-compound is of the same order as the combined amounts of nitro-alcohol and nitro-nitrate (both derived from nitro-nitrite). Oxygen addition tends to favour the last component to a marked extent.

*Discussion.*—Under the reaction conditions employed, addition of tetroxide takes only two forms : (i) as two nitro-groups, giving dinitro-compounds, and (ii) as one nitro- and one nitrite group, giving nitro-nitrites which ultimately yield the corresponding nitro-alcohols and nitro-nitrates. Ordinarily, the two forms of addition occur to a similar extent and only the use of relatively large quantities of oxygen effects any drastic change in their proportion. For unsymmetrical olefins, the second mode of addition always results in attachment of the nitro-group to the carbon with the greater number of hydrogen atoms and the nitrite group to that with the smaller number. No evidence has been obtained in any case for the reverse mode of addition or for the addition of two nitrite groups. The formation of minor, if troublesome, amounts of nitro-nitroso-compounds (nitrosites) has been shown to occur only when dinitrogen trioxide is present or allowed to form in the course of uncontrolled oxidation reactions. Nitroso-nitrates have not been found and, since it is usually possible to account for the reagents almost quantitatively by (i) and (ii) above, together with experimentally verified extraction losses, it is reasonable to conclude that these other modes of addition do not occur to a significant degree. The main reaction may therefore be regarded as one between the activated double bond $>C{=}\overset{\curvearrowright}{C}<$ and forms of the tetroxide expressed for the time being as $(-NO_2)(-NO_2)$ and $(-NO_2)(-ONO)$. It is suggested that both additions are polar and involve the same initial attack by the electropositive nitrogen of the nitro-group.

The structure of the active tetroxide molecule is still uncertain, chemical evidence suggesting both forms (A) and (B). Although the *X*-ray evidence is said to support (A) and to indicate an abnormally long N–N



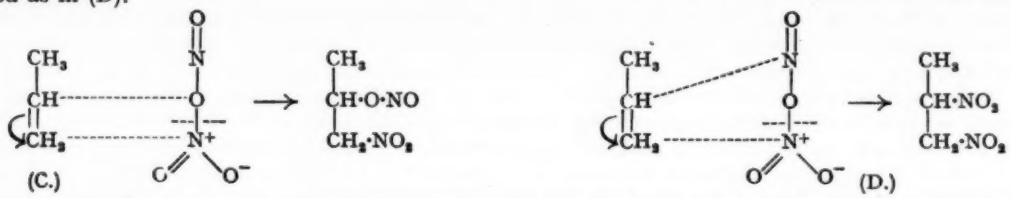
(A.)



(B.)

distance, yet the balance of past chemical evidence is thought to favour (B), which can give rise by appropriate fission to nitro-, nitrite, nitroso-, and nitrate groups and therefore to a variety of modes of action of the tetroxide. Since the present series of investigations establishes that only nitro- and nitrite groups are involved, they cannot be said to favour either of the two possible structures. Formation of nitro-nitrate is relatively small in the absence of oxygen and cannot therefore be regarded as indicating (B). The directive influence noted with unsymmetrical olefins, the specific solvent effect with the intermediate olefins in the series, and perhaps also the effect of oxygen, all suggest a polar mechanism for the addition reactions, the first step in which appears to be the attachment of the electropositive nitrogen to the activated carbon atom, the second nitro-group being attached either by C–N or C–O linkage to the other side of the double bond. Propylene, for example, would

give the required nitro-nitrite as shown in (C), whereas the dinitro-compound may similarly be supposed to be formed as in (D).



(C.) (D.)

In this connection, it is noteworthy that dinitrogen trioxide in ether yields both nitro-nitroso-compounds and the normal products of tetroxide addition in substantial amount. The nitro-nitroso-compounds formed from propylene and *iso*butylene follow a rule similar to that shown by nitro-nitrites, the nitroso-group, like the nitrite group, becoming attached to the carbon with fewer hydrogen atoms. Whatever the constitution of the trioxide in these circumstances, these results suggest an equilibrium between dissolved and combined NO, in turn giving rise to structures of the type $\overset{+}{N}O_2\}X$, where X is either form of $NO_2$ or NO. Addition of all these assemblies appears to be polar and to proceed by the same initial step. The general reaction can thus be written :

$$>C{=}C< + \overset{+}{N}O_2X \longrightarrow >\overset{\bullet}{C}-\overset{|}{C}\cdot NO_2 \ldots . X \longrightarrow >CX-\overset{|}{C}\cdot NO_2 \quad (X = NO_2, O\cdot NO, NO)$$

That dinitrogen tetroxide can also act as an oxidising agent and thus give rise to the trioxide is of course to be expected, though this tendency should be limited at the low temperatures employed (−10° to +25°). The interfering effects of the trioxide can be eliminated by one or more of the following : (*a*) excess of tetroxide, (*b*) high concentrations of tetroxide, (*c*) use of oxygen, through which the concentration of the trioxide becomes unimportant. The tendency to oxidise varies with the olefin; thus, ethylene, the trimethylpentenes, and *cyclo*hexene are little oxidised, even when reacting with pure liquid tetroxide, whereas propylene and *iso*butylene in these circumstances give rise to aqueous nitric acid, water-soluble oxidation products and the nitrate of the α-hydroxycarboxylic acid, $CHMe(O\cdot NO_2)\cdot CO_2H$ and $CMe_2(O\cdot NO_2)\cdot CO_2H$. Dinitroparaffin is apparently not formed, although the survival of the carboxyl group suggests a single C–N linkage initially, followed by hydrolysis of the primary $CH_2\cdot NO_2$ group. With ether- or ester-type solvents, depending on electron availability at the oxygen bridge, the oxidation reactions are largely prevented, even in very concentrated solutions (*e.g.*, 50% tetroxide by weight in diethyl ether), thus permitting formation and survival of the normal addition products. The isolation of the dioxan–dinitrogen tetroxide complex, and the gradation of solvent effect with the nature of the side groups about the oxygen bridge, seem to establish that these solvents act by molecular association with the tetroxide, increasing its polarity and facilitating initial attack by the $\overset{+}{N}O_2$ group. The balance between the two normal modes of addition does not appear to be affected by the solvent, from which it may be suggested that solvent–tetroxide association takes the form of $A \ldots \overset{+}{N}O_2X$ where A is solvent and X the second group :

$$>C{=}CH_2 + A \ldots \overset{+}{N}O_2\}X \longrightarrow >\overset{\bullet}{C}-\underset{X}{CH_2}\cdot NO_2 \ldots A \longrightarrow >CX-CH_2\cdot NO_2 + A \quad (X = NO_2, O\cdot NO, NO)$$

Oxygen was originally fed to the reaction in minor quantities to reduce trioxide formation and hence provide a product more stable to distillation. Two further effects have, however, been found : (i) it increases the formation of nitro-nitrate, by assisting the oxidation of nitro-nitrite; with ethylene, the amount of oxygen absorbed corresponds closely to the amount of nitroethyl nitrate formed, (ii) at least in the case of *iso*butylene, it increases the total yield of products derived from nitro-nitrite at the expense of the dinitro-compound. No satisfactory explanation of the latter effect can yet be offered.

More detailed description of the procedures with individual olefins is given in later papers, together with an account of the characterisation, properties, and chief reactions of the main products, many of which are new and have proved to be of unusual interest. For some of the compounds made, special analytical methods were necessary, and these will be described subsequently.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RESEARCH DEPARTMENT, BILLINGHAM, CO. DURHAM.

[*Received, April 2nd,* 1946.]

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## 241. *Addition of Dinitrogen Tetroxide to Olefins. Part II. Ethylene.*

By NORMAN LEVY, CHARLES W. SCAIFE, and ARTHUR E. WILDER SMITH.

Ethylene can be nitrated with liquid or dissolved dinitrogen tetroxide, preferably with addition of gaseous oxygen, to give high overall yields, *i.e.*, 70—80% on ethylene, of pure separated products. The reaction must be controlled below room temperature. Ethylene reacts much more slowly than the higher olefins, and best results are given by absorbing 0·4 mol. of ethylene per mol. of tetroxide during approximately 10 hours. It has been

established that addition follows only two paths: (i) as two nitro-groups to give 1 : 2-*dinitroethane*, and (ii) as one nitro-group and one nitrite group to give the *nitrite* of 2-nitroethanol. This ester is extremely unstable, especially in the last stages of removing excess of dinitrogen tetroxide from the reaction product, and is best converted into the nitro-alcohol by reaction with methanol at an early stage in separation. On cooling, the methanol solution deposits solid 1 : 2-dinitroethane, m. p. 39—40°, in 35—40% yield, and nitroethanol and its nitrate (formed in the main reaction by oxidation of part of the nitrite) are separated by water–benzene extraction, each in 12—20% yield. Some of the properties and derivatives of the three products are described, and 1 : 2-dinitroethane is adequately characterised for the first time.

WORK on the nitration of olefins with dinitrogen tetroxide began with ethylene, and most of the general problems of olefin nitration were solved in its investigation, though it eventually proved to be the least tractable of the olefins, the addition reaction being much slower and the initial products less stable than with higher homologues. The literature on the nitration of ethylene with oxides of nitrogen is somewhat conflicting and describes various single products without accounting for the bulk of the reactants. Semenoff (*Jahresber.*, 1864, 480; *Z. Chem. Pharm.*, 1864, **7**, 129) made careful examination of the reaction between dry ethylene and dry tetroxide (made by heating dry lead nitrate) in the gas phase at 60—70°, in the liquid phase, and in ethereal solution, and in the last case was able to crystallise from the solution a white solid, m. p. 37·5°, which he called " ethylene dinitrite." The present work clearly shows that the solid was in fact 1 : 2-*dinitroethane*, m. p. 39—40° when pure, and that it represents only about half of the product from liquid-phase reaction. The remainder gives rise to 2-nitroethanol and its nitrate by the treatment outlined in the preceding paper. Although these are not new substances (Wieland and Sakellarios, *Ber.*, 1920, **53**, 201; McKie, *J.*, 1927, 962) they have not been previously obtained by nitration of ethylene with the tetroxide or " nitrous gases."

Demjanow (*Ann. Inst. Agron. Moscow*, 1894, **4**, 155) obtained " ethylene nitrosite," m. p. 116—117°, from the reaction between ethylene and " nitrous fumes " in ether. Sidorenko (*J. Russ. Phys. Chem. Soc.*, 1913, **45**, 1585), who repeated this preparation, stated that examination of residual products in the ether was dangerous since they invariably exploded during concentration of the solution. The reaction between ethylene and dinitrogen trioxide in ether and other inert solvents to give " ethylene nitrosite," for use as a secondary charge in blasting caps and primers, has been patented (Marshall, U.S.P. 1,473,825, 1921). Harris and Siegel (*J. Amer. Chem. Soc.*, 1941, **63**, 2520) found no reaction between ethylene and gaseous tetroxide in the dark at room temperature, but under the influence of ultra-violet light ethylene oxide and acetaldehyde were formed.

The present work shows, in confirmation of Semenoff's results, that reaction in the vapour phase does occur and that 1 : 2-dintroethane can be isolated from the products. Even at 100°, this can be formed, but above 150° a chain oxidation reaction sets in and may become explosive. Liquid-phase reaction, using either pure tetroxide or a solution, is much more satisfactory in that it leads to simpler products in high total yield; by the methods here described the recoveries of pure products are 35—40% of 1 : 2-dinitroethane, 12—20% of 2-nitroethanol and 12—20% of 2-nitroethyl nitrate, all based on ethylene absorbed. The 1 : 2-dinitroethane obtained and characterised beyond doubt is quite different from the greenish-yellow oil, b. p. 94—96°/5 mm., prepared by Ipatov (*J. Russ. Phys. Chem. Soc.*, 1917, **49**, 297) by reaction between silver nitrite and ethylene iodide.

*Nitration Procedure.*—The reaction is carried out by passing dry ethylene into pure liquid or dissolved dinitrogen tetroxide, cooled by a bath at 0°. Reaction is quite slow compared with that of other olefins, and at least 10 hours are required for the optimum absorption of ethylene, which is found to be 0·4 mol. per mol. of tetroxide. With higher proportions of ethylene, the yield of nitrated products per mol. of ethylene diminishes. The initial addition products are 1 : 2-dinitroethane (I) and 2-nitroethyl nitrite (II), while a portion of the latter is oxidised to the nitrate (III) by the tetroxide which in turn gives rise to trioxide :

$$\underset{\text{(I.)}}{NO_2\cdot CH_2\cdot CH_2\cdot NO_2} \xleftarrow{N_2O_4} CH_2{:}CH_2 \xrightarrow{N_2O_4} \underset{\text{(II.)}}{NO\cdot O\cdot CH_2\cdot CH_2\cdot NO_2} \xrightarrow{N_2O_4} \underset{\text{(III.)}}{NO_2\cdot O\cdot CH_2\cdot CH_2\cdot NO_2} + N_2O_3$$

Side reactions due to trioxide can be avoided by passing oxygen into the reaction mixture during ethylene absorption, usually at about 20—30% of the ethylene rate. As well as keeping the tetroxide fully oxidised, the use of oxygen produces a more stable nitration product. Analysis of the gases leaving the reaction vessel shows that very little oxidation of ethylene to oxides of carbon occurs. Yields are not increased by addition of dehydrating agents, *e.g.*, sulphuric acid, phosphoric oxide, or anhydrous copper sulphate, although moisture appears to have a deleterious effect through formation of the trioxide.

The ethylene is preferably introduced through a sintered-glass plate. Although the speed of absorption is increased with a spinning gas distributor, the nitration rate is hardly affected. In small-scale experiments considerable absorption of products occurs in the sintered plate, which should be extracted with methanol for good recoveries. Benzene, carbon tetrachloride, ethyl ether, and dioxan have been studied as reaction solvents, and the same three products obtained in each case. When oxygen is not used, the ether class of solvents decreases the proportion of nitrate formed by moderating the oxidising character of the tetroxide. This observation is in line with the rôle of ether or ester solvents in the nitration of propylene and the butylenes where such solvents appear to be essential for dinitroparaffin formation.

*Separation Procedure.*—After completion of absorption to the optimum molar ratio, excess of tetroxide is removed by a current of dry air, nitrogen, or carbon dioxide, or by evaporation under reduced pressure, and is recovered by condensation as solid in receivers cooled to −70°. Care should be taken to keep the crude

nitration product cold, *i.e.*, at about 0°, in the final stages of removal of tetroxide since the nitro-nitrite is very unstable when free from tetroxide or solvent. Although batches exceeding 1 kg. of crude product have been satisfactorily handled in this manner, it is preferable to evaporate continuously from a warm falling film in the manner applied to other olefins and described in the previous paper (see British Patent Application No. 17,160/45). This avoids the risk of accumulating a large volume of unstable product and permits it to fall dropwise into cold methyl alcohol where the 2-nitroethyl nitrite is immediately converted into the stable 2-nitroethanol, methyl nitrite being evolved: $NO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NO_2 + CH_3{\cdot}OH \longrightarrow OH{\cdot}CH_2{\cdot}CH_2{\cdot}NO_2 + CH_3{\cdot}O{\cdot}NO$. This mechanism has been confirmed by (i) condensing and identifying the methyl nitrite formed, (ii) proving that the quantity of nitrite in the crude oil corresponds to the amount of nitro-alcohol formed, (iii) isolating somewhat impure nitroethyl nitrite by very careful fractional distillation of the crude oil, (iv) preparing nitroethyl nitrite from nitroethanol and converting it back into nitroethanol by treatment with methyl alcohol. It has been shown, in addition, that the nitrite is slowly oxidised to the nitrate ester by liquid tetroxide and oxygen.

About 1½—2 vols. of methyl alcohol per vol. of crude oil are used and the solution, which now contains dinitroethane, nitroethanol, and nitroethyl nitrate is cooled with stirring in a bath of solid carbon dioxide-methanol. Crystalline 1 : 2-dinitroethane is deposited, and filtered off for recrystallisation from methanol or benzene. The separation is assisted by the presence of the nitroethanol, which prevents deposition of the nitrate and consequent interference with the crystallisation of 1 : 2-dinitroethane. Methyl alcohol is evaporated from the filtrate under reduced pressure, leaving a mixture of nitroethanol and nitroethyl nitrate containing a small quantity of dissolved dinitroethane. This mixture is best separated by stirring with benzene and water; the nitrate and the dinitroethane pass into the benzene, and the nitroethanol into the water for later extraction with ether. After removal of the solvents, the nitroethyl nitrate and nitroethanol are purified by fractional distillation under high vacuum. The crude products attack the skin and direct contact should be avoided; dinitroethane and nitroethyl nitrate also give rise, when crude, to highly lachrymatory nitroethylene, and hence the separation stages involved should be carried out in an efficient fume cupboard, which also affords safe release of the toxic methyl nitrite formed by alcohol treatment.

*Yields.*—The total yield of pure products accounts for at least 70% of the ethylene and 80% of the tetroxide. In the example described later, the amounts of the three pure products isolated correspond to the following percentages on the reagents consumed:

| | Yield % on $C_2H_4$. | Yield % on $N_2O_4$. |
|---|---|---|
| 1 : 2-Dinitroethane ..... | 36·9 (38·7) | 41·5 (43·6) |
| 2-Nitroethanol ..... | 16·4 (20·5) | 18·4 (23·0) |
| 2-Nitroethyl nitrate ..... | 20·2 (28·0) | 22·8 (31·5) |
| Totals ..... | 73·5 (87·2) | 82·7 (98·1) |

Parallel experiments applying the entire separation procedure to synthetic mixtures indicate losses of the order of 5%, 20%, and 28%, respectively, for the three components, and the figures in parentheses are corrected percentages for the untreated product mixture. These are sufficiently close to quantitative values to indicate that, under the given reaction conditions, addition of dinitrogen tetroxide to ethylene takes only the two courses mentioned on p. 1097, other modes, *e.g.*, dinitrite or nitroso-nitrate addition, not occurring to any significant extent.

It is noteworthy that the oxygen absorbed is usually equivalent to the nitroethyl nitrate formed; referring to the example given later, 32·5 g. of oxygen were absorbed, whereas 30·8 g. are required for the oxidation of the nitroethyl nitrite (*via* the tetroxide) to the 261·7 g. of nitroethyl nitrate isolated. Also of interest is the observation that 1 : 2-dinitroethane is obtained by reaction of ethylene and tetroxide in the vapour phase at approximately 100°. As might be expected, the yields of nitroethanol and nitroethyl nitrate are low under these conditions.

*Properties and Reactions.*—Some of the physical and explosive properties and chemical reactions of the products are described below. It is hoped to deal more fully with the reactions of dinitroparaffins, nitro-alcohols, and the nitrates in later publications.

1 : 2-*Dinitroethane.*—This is a white crystalline solid, m. p. 39—40° after recrystallisation from methanol or benzene; it distils under high vacuum to give a clear colourless liquid, b. p. 88°/*ca.* 1 mm. Molten 1 : 2-dinitroethane is easily supercooled and may be kept liquid even at 0°; shaking, scratching, or seeding causes immediate solidification with evolution of heat. The solid slowly decomposes on storage, turning yellow, becoming liquid, and finally decomposing after several weeks with the production of nitrous fumes, some nitroethylene, and a tarry liquid residue. It readily loses nitrous acid in the presence of alkali: $NO_2{\cdot}CH_2{\cdot}CH_2{\cdot}NO_2 + NaOH \longrightarrow NaNO_2 + H_2O + CH_2{:}CH{\cdot}NO_2 \longrightarrow$ polymer. Even very weak bases promote this reaction, which may be carried out with ammonia, the carbonates and bicarbonates of the alkali and alkaline-earth metals, urea, and some heavy-metal oxides such as zinc oxide. "Pyrex" containers are therefore preferable to ordinary soda-glass bottles for storage. The dispersion of a small amount of aromatic sulphonic acid in the melt greatly increases the stability of 1 : 2-dinitroethane, and samples containing 0·5% of the 1 : 5-disulphonic acids of either naphthalene or anthraquinone have been stored both at room temperature and at 50° for a year without appreciable change.

1 : 2-Dinitroethane is a powerful explosive, showing a power of 91·1% blasting gelatin in the mortar test.

It is insensitive to friction and impact, but is also very insensitive to initiation. It has been characterised by reduction to ethylenediamine and by mineral acid hydrolysis to hydroxylamine and oxalic acid.

2-*Nitroethanol*.—When pure, this is a colourless mobile liquid, b. p. 63°/*ca.* 0·5 mm., 102°/*ca.* 11 mm., $d_4^{20°}$ 1·296, $n_D^{20°}$ 1·443. It is somewhat hygroscopic. Although stable to storage and distillation when pure, care is essential in distilling impure samples at the beginning and end of distillation. It has an explosive power of 61·1% blasting gelatin and is very insensitive to friction, impact, and initiation.

2-Nitroethanol can be dehydrated to give monomeric nitroethylene which, however, instantly polymerises in the presence of a trace of alkali. It has been reduced to ethanolamine and has been further characterised through its esters and trityl ether and by comparison with 2-nitroethanol prepared by Wieland and Sakellarios's method (*loc. cit.*).

2-Nitroethyl nitrate, when pure, is a colourless mobile liquid, b. p. 74°/*ca.* 1 mm., $d_4^{20°}$ 1·446, $n_D^{20°}$ 1·455. It can be distilled under high vacuum, withstands heating in a vacuum at 100° for more than 20 hours, and has been stored at room temperature for more than two years without appreciable deterioration. It is a powerful explosive, giving values of 102% blasting gelatin in the mortar test when mixed with 7% soluble blasting gun-cotton. It is very insensitive to friction and impact, but can be detonated to high velocity. Like dinitroethane, it is converted by molar quantities of alkali into polymeric nitroethylene: $NO_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}NO_2 + NaOH \longrightarrow NaNO_2 + H_2O + CH_2{:}CH{\cdot}NO_2 \longrightarrow$ polymer. It has been hydrolysed to nitroethanol and nitric acid and is further characterised by comparison with nitroethyl nitrate prepared according to Wieland and Sakellarios (*loc. cit.*).

## Experimental.

*Reagents*.—Crude liquid dinitrogen tetroxide was obtained by refrigeration of gas from an ammonia-oxidation plant and rigorously purified by fractional distillation in a stream of oxygen at 30° to eliminate lower oxides and dissolved nitric acid. Nitric acid spray and moisture were removed from the vapour by passage through silica gel and phosphoric oxide. The pure substance was condensed as a clear white solid in receivers cooled to −70° by solid carbon dioxide–methanol. The receiver outlets were fitted with phosphoric oxide and calcium chloride drying tubes to prevent ingress of atmospheric moisture. Liquid tetroxide was obtained on allowing it to warm to room temperature and was stored in closed pressure bottles of glass or stainless steel.

Ordinary commercial ethylene and oxygen, both of sufficiently high purity, were taken from cylinders and dried by passage through calcium chloride before being mixed and delivered to the reaction vessel.

*Nitration Apparatus and Method*.—Standard batch preparations were made with a quantity of 3 l. of liquid tetroxide (about 4500 g.) contained in a round-bottomed 5-l. "Pyrex" flask cooled by a bath at 0°. Ethylene at 30 l./hr. and oxygen at 8 l./hr. were measured through rotary gas-meters, the volumes being corrected to atmospheric pressure by reference to manometers attached to the gas lines. After being dried and mixed, the gases were passed for 10½ hours into the liquid tetroxide through a sintered-glass spoon. Exit gases from the reaction flask were passed through receivers at −70° to trap the tetroxide, the volume then measured by rotary gas-meters, and the composition determined by gas analysis. Ground glass joints were used throughout and, where flexibility was necessary, *e.g.*, in the connection between reaction flask and tetroxide traps, joints were of the ball-and-socket type.

Out of 347·9 l. of ethylene passed, 228·5 l. were absorbed, the corresponding figures for oxygen being 81·3 and 24·4 l., respectively, all volumes being corrected to 20° and 760 mm. The amounts absorbed were in close agreement with the difference between the initial weight of tetroxide and the combined weight of the final reaction mixture and the tetroxide trapped.

Excess of tetroxide was removed from the reaction mixture by bubbling with dry air, and recovered by cooling to −70°; special care was taken to keep the mixture cool with a bath at 0° during the last stages of its removal. The residual pale yellow oil weighed 1153 g., which, reckoned completely as $C_2H_4O_4N_2$, represented an almost theoretical yield of crude oil on the ethylene absorbed.

*Separation and Purification of Products*.—The crude oil, which showed slow gas evolution, was added to 2 l. of methyl alcohol with stirring and cooling in a bath of solid carbon dioxide–methyl alcohol. On filtration, 408·4 g. of solid 1 : 2-*dinitroethane* were obtained. A further 13 g. were deposited from a second cooling. The yield on ethylene absorbed was 36·9%, and on tetroxide consumed 41·5%. Analysis after recrystallisation from methyl alcohol gave C, 20·1; H, 3·5; N, 23·2 ($C_2H_4O_4N_2$ requires C, 20·0; H, 3·3; N, 23·3%).

Methyl alcohol was distilled from the filtered solution, first at 15 mm. and finally at 1 mm. and 40°, leaving 613 g. (440 ml.) of a stable oil. This was subjected to double solvent washing by stirring with a mixture of 2·2 l. of benzene and 2·2 l. of water for a total period of 4 hours. Nitroethanol, which is practically insoluble in benzene, passed wholly into the water layer, and the nitroethyl nitrate into the benzene layer. Were it nor for the presence of small amounts of nitric acid, simple separation of the two layers would have sufficed, but this impurity necessitated intermittent withdrawal of the water layer for partial neutralisation so as to minimise solution of nitroethyl nitrate in the aqueous layer. Almost complete separation of the two components was achieved in this manner, with a final neutralisation of the aqueous layer before taking it off.

The aqueous layer was extracted continuously with ether for 48 hours, the ethereal extract dried ($Na_2SO_4$), and the ether distilled off at reduced pressure. The crude nitroethanol was fractionally distilled at *ca.* 1 mm. to give 142·2 g. of 2-nitroethanol and 13·1 g. of residue. The yield on ethylene was 16·4%, and on tetroxide 18·4%. Analysis after vacuum redistillation was C, 26·3; H, 5·6; N, 15·5 (Calc. for $C_2H_5O_3N$: C, 26·4; H, 5·5; N, 15·4%).

The benzene layer was dried and the benzene distilled off. The resulting oil was fractionally distilled at *ca.* 1 mm. to give 261·7 g. of 2-nitroethyl nitrate and 56·0 g. of residue, consisting partly of nitrate and partly of dinitroethane which are not included in the yields, but gave 14·3 g. dinitroethane on freezing in a large volume of methanol. The yield of nitroethyl nitrate on ethylene was 20·2% and on tetroxide 22·8%. Analysis after redistillation gave C, 20·7; H, 3·0; N, 17·9 (Calc. for $C_2H_4O_5N_2$: C, 20·6; H, 2·9; N, 17·7%).

Vacuum distillations of crude nitroethanol and crude nitroethyl nitrate required particular care, *i.e.*, slow rate of boiling, use of a dry carbon dioxide leak in place of the usual air leak, and occasional rapid cooling of the boiler with a solid carbon dioxide–methanol mixture kept at hand for use whenever gas evolution was marked. Redistillation of once-distilled materials, was, on the other hand, quite smooth and without difficulty.

*Preparation of Derivatives*.—Reduction of 1 : 2-dinitroethane to ethylenediamine was carried out in glacial acetic acid by using Adams's platinum catalyst and hydrogen at 80—100 atm. At concentrations above 2·6 g. of dinitroethane per 100 ml. of acetic acid, yields tended to be low apparently through interaction of amine and primary nitro-group,

despite the use of an acid solvent. In one experiment 0·269 g. of dinitroethane in 45 ml. of glacial acetic acid was reduced at 90 atm. in the presence of 0·022 g. of catalyst. The acetic acid was then saturated with dry hydrogen chloride and distilled off, leaving ethylenediamine dihydrochloride which was washed with ethyl alcohol; yield 0·261 g., 87·6% (Found: C, 18·1; H, 7·4; N, 20·2; Cl, 54·5. Calc. for $C_2H_{10}N_2Cl_2$: C, 18·0; H, 7·5; N, 21·0; Cl, 53·4%).

Hydrolysis of 1 : 2-dinitroethane was best carried out by heating it with mineral acids other than nitric in a sealed tube at 150°. Hydrochloric, sulphuric, phosphoric, and even sulphonic acids could be used, but the highest yields were given by concentrated hydrochloric acid and 13 mins.' heating: the best method was to heat 0·301 g. of dinitroethane with 4·5 ml. of the acid, cool the mixture, and dilute it with 200 ml. of distilled water for analysis. One portion of the solution was boiled with at least 100% excess of ferric salt, air being excluded, and the ferrous ion titrated with standard dichromate, using an internal indicator, to give the hydroxylamine content. The result was confirmed on another portion by precipitating the hydroxylamine as copper salicylaldoxime complex (Ephraim, *Ber.*, 1930, **63**, 1928), regenerating hydroxylamine from the complex by boiling it with sulphuric acid, and estimating it as before. The estimated yield was 90·8% on the basis of 2 mols. of hydroxylamine per mol. dinitroethane. Oxalic acid was determined on a third portion by neutralising it with ammonia, precipitating calcium oxalate, and titrating with N/10-permanganate. Despite the heating to 150°, the yield was 47·3%.

*Esters and Trityl Ether of 1-Nitroethanol.*—The acetate, benzoate, and *p*-nitrobenzoate were prepared by reaction with the acid chlorides. Properties were as follows: Acetate, liquid, b.p. 70°/<1 mm. (Found: C, 36·3; H, 5·5; N, 10·8. Calc.: C, 36·1; H, 5·3; N, 10·5%); benzoate, m. p. 42—44°; *p-nitrobenzoate*, m. p. 100° after recrystallisation from ethyl alcohol (Found: C, 44·9; H, 3·4; N, 11·7. $C_9H_8O_6N_2$ requires C, 45·0; H, 3·3; N, 11·7%).

The *trityl ether* was prepared by refluxing 2 g. of 2-nitroethanol with 6·1 g. of triphenylmethyl chloride in 40 ml. of benzene for 11 hours. Part of the benzene was removed, the solution cooled, and 4·9 g. of crystals filtered off. After three recrystallisations from benzene, the ether had m. p. 162—164° (Found: C, 74·6; H, 5·8; N, 4·6. $C_{21}H_{19}O_3N$ requires C, 75·6; H, 5·7; N, 4·2%); the mixed m. p. with the ether (m. p. 160—162°) prepared from synthetic 2-nitroethanol was 160—162°.

Reduction of 2-nitroethanol to ethanolamine could be carried out in glacial acetic acid as for dinitroethane. Reduction in ethyl alcohol, however, permitted the preparation of more distinctive derivatives, *e.g.*, the picrate: 2·79 g. in 25 ml. of absolute alcohol were reduced at 100 atm. in the presence of 0·201 g. of Adams's catalyst for 5 hours, the catalyst filtered off, 6·8 g. of picric acid added, and the solution warmed and filtered; on standing overnight, 3·95 g. (44·4%) of the picrate were obtained; recrystallisation gave m. p. 157—159°, whereas the picrate obtained in identical manner from synthetic 2-nitroethanol (Wieland and Sakellarios, *loc. cit.*) had m. p. 157—160° and this was also the mixed m. p.

*Polymeric nitroethylene from 2-nitroethanol nitrate.* Both 1 : 2-dinitroethane and nitroethyl nitrate gave polymeric nitroethylene in good yield on reaction with alkali; *e.g.*, 10 g. of the nitrate were dissolved in 100 ml. of methanol and added with brisk stirring during 3 minutes to 6·7 g. of ammonium hydrogen carbonate dissolved in 100 ml. of water. The lachrymatory nitroethylene monomer first formed rapidly polymerised and, after 30 minutes' stirring, the polymer was filtered off, washed with dilute hydrochloric acid and water, and dried in a vacuum over phosphoric acid; yield 5·1 g. (84%) [Found: C, 32·9; H, 4·2; N, 19·1. Calc. for $(C_2H_3O_2N)_n$: C, 33·1; H, 4·2; N, 18·9%].

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## 242. *Addition of Dinitrogen Tetroxide to Olefins. Part III. Propylene.*

By NORMAN LEVY and CHARLES W. SCAIFE.

The addition of dinitrogen tetroxide to propylene to give 1 : 2-*dinitropropane* and β-nitro*iso*propyl nitrite requires an ether or ester solvent as reaction medium; otherwise, oxidation reactions supervene and the only product isolated is the nitrate ester of lactic acid. When using an excess of the tetroxide in ether, the reaction is at least 3—4 times as fast as that with ethylene, but the modes of addition are similar, *i.e.*, as two nitro-groups and as one nitro- and one nitrite group. With the latter mode of addition, the nitrite group is attached to the carbon with the fewer hydrogen atoms, and the nitro-nitrite so formed is partly oxidised to nitro-nitrate. Like all the lower members of the series, the nitro-nitrite is unstable and should be converted into nitro-alcohol by water treatment for safe and efficient separation of the nitrated products. When oxygen is added to the reaction mixture, the total yield on propylene is about 75% made up of 33% as β-nitro*iso*propanol, 21% as 1 : 2-*dinitropropane*, and 21% as *β-nitroisopropyl nitrate*, and instability and separation difficulties due to addition of dinitrogen trioxide are avoided. In the absence of oxygen, nitro-nitrate formation is small but substantial amounts of 4-nitro-3-methylfurazan oxide are formed, probably *via* nitroacetone oxime, and interfere with separation of the main products. Both 1 : 2-dinitropropane and β-nitro*iso*propyl nitrate are new, and their reactions are briefly described. Although both 1 : 2-dinitroethane and 1 : 2-dinitro*iso*butane are solid above room temperature, 1 : 2-dinitropropane is liquid even at − 40°, possibly because it is the *dl*-form.

THERE is little previous work on the addition of oxides of nitrogen to propylene and none specifically referring to the tetroxide. Demjanow (*J. Russ. Phys. Chem. Soc.*, 1901, **33**, 275) treated propylene with nitrous fumes (from arsenious oxide and nitric acid) in ethereal solution and obtained propylene " nitrosite " as a white solid, m. p. 119—120°, identified by reduction to the propylenediamine. Marshall (U.S.P., 1,473,825, 1921) covered the reaction between propylene and dinitrogen trioxide in ether and other inert solvents to give propylene " nitrosite " for use as a secondary charge in blasting caps and primers. The present work has shown that nitro-nitroso-addition is only of minor importance with the tetroxide and may under appropriate conditions be avoided altogether, while even the trioxide, behaving partly as such and partly as tetroxide, gives less simple products than was thought.

Straightforward addition of the tetroxide to propylene to give 1 : 2-*dinitropropane*, and β-*nitroisopropyl nitrite* does not occur unless an ether or ester solvent is used as reaction medium. When propylene is passed into pure liquid dinitrogen tetroxide in the manner described for ethylene (Part II, preceding paper), rapid

reaction occurs and the mixture soon becomes green owing to reduction of the tetroxide. After removal of unreacted tetroxide, a stable liquid product remains which, since it is completely soluble in water, contains no dinitropropane or nitropropyl nitrate. A clear, almost water-white liquid is obtained by ether extraction and distillation. It deposits needle crystals of the nitrate of lactic acid, $CH_3{\cdot}CH(O{\cdot}NO_2){\cdot}CO_2H$, on standing. The manner in which this compound is formed has not been investigated, but it is likely to arise from the oxidation of β-*nitroisopropyl nitrate*. It has previously been prepared by the action of sulphuric and fuming nitric acids on zinc lactate (Duval, *Compt. rend.*, 1903, **137**, 1263).

When, however, propylene is passed into a solution of the tetroxide in ether or dioxan, the oxidising character of the oxide is moderated and the two types of addition usual in this series take place: (*a*) as two nitro-groups to give 1 : 2-dinitropropane (I), and (*b*) as one nitro- and one nitrite group, the latter becoming attached as expected to the carbon with the fewer hydrogen atoms, to give β-nitro*iso*propyl nitrite (II). Part of the latter is oxidised to the nitro-nitrate (III) in the course of reaction, the amount being sharply increased when oxygen is added with the propylene.

$$CH_3{\cdot}CH(NO_2){\cdot}CH_2{\cdot}NO_2 \xleftarrow{N_2O_4} CH_3{\cdot}CH{:}CH_2 \xrightarrow{O{\cdot}NO{\cdot}NO_2} CH_3{\cdot}CH(O{\cdot}NO){\cdot}CH_2{\cdot}NO_2 \xrightarrow{\text{Oxidn.}} CH_3{\cdot}CH(O{\cdot}NO_2){\cdot}CH_2{\cdot}NO_2$$
(I.) (II.) (III.)

In common with all the lower member of the series, the nitro-nitrite is unstable and it is therefore advisable to treat the crude reaction product with water, after removal of excess tetroxide and solvent, to convert the nitro-nitrite (II) into the stable β-nitro*iso*propyl alcohol, $CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}NO_2$. Although the latter had been prepared by Henry (*Bull. Soc. chim.*, 1895, **13**, 999) by condensing nitromethane with acetaldehyde, both (I) and (III) are new. The total yield of separated products on propylene is 70—75%, with 20—30% as dinitropropane, 35—40% as nitro-propanol, and 2—20% as nitro*iso*propyl nitrate, the proportions depending on the use of oxygen, which not only increases the amount of the nitrate but also prevents interference by dinitrogen trioxide addition, particularly the formation of 4-nitro-3-methylfurazan oxide (VII).

The last substance can be formed to the extent of 5—8% on the propylene consumed, when no oxygen is added to the reaction. It is formed in greater amount when dinitrogen trioxide is used in place of the tetroxide together with dinitropropane and nitropropanol, and only a small amount of nitronitrosopropane can be isolated. For these reasons the following stages in its formation are suggested: (i) addition of trioxide to propylene to give 1-nitro-2-nitrosopropane (IV) which rearranges to nitroacetone oxime (V), and (ii) condensation of the latter with nitrous acid to give the dioxime (VI) followed by dehydration and oxidation to the furazan oxide:

$$CH_3{\cdot}CH{:}CH_2 \xrightarrow{N_2O_3} \underset{\text{(IV.)}}{CH_3{\cdot}CH(NO){\cdot}CH_2{\cdot}NO_2} \longrightarrow \underset{\text{NOH}}{CH_3{\cdot}\overset{|}{C}{\cdot}CH_2{\cdot}NO_2} \text{ (V.)} \xrightarrow{HNO_2}$$

$$\underset{\text{(VII.)}}{CH_3{\cdot}C{=}C{\cdot}NO_2\ (N,N,O,O)} \xleftarrow{\text{Oxidn.}} CH_3{\cdot}C{=}C{\cdot}NO_2\ (N,N,O) \xleftarrow{-H_2O} \underset{\text{(VI.)}}{CH_3{\cdot}\overset{|}{C}{=}\overset{|}{C}{\cdot}NO_2\ (\text{NOH, NOH})}$$

*Nitration Procedure.*—The apparatus is similar to that described in Part II (see British Patent Application No. 6147/44). Dry propylene is absorbed in a concentrated solution of dinitrogen tetroxide in dry ether or ester solvent. Sodium-dried ethyl ether is the most suitable solvent, and normally the concentration of tetroxide is limited to 40% by weight in order to minimise oxidising side reactions. Reaction temperatures of −10° to 25° can be employed with ether as solvent, 0—10° being the preferred range for batch preparations. Still higher temperatures are available with dioxan, since complex formation with the tetroxide then reduces its evaporation. The tendency of the solid complex to separate and also to form in the gas-exit lines makes dioxan a less convenient solvent than ether.

Absorption can be taken to completion (1 mol. of propylene to 1 mol. of dissolved tetroxide) but an excess of the latter is desirable to check formation and addition of trioxide. The absorption rate is at least 3—4 times as fast as that with ethylene, 40% of theoretical being taken up in 3 hours, compared with 10½ hours for ethylene. Still faster rates may be used. Heat is evolved during the reaction and the mixture must be kept cool in an ice-bath. In the absence of oxygen, the mixture soon loses its pale amber colour and turns green, with formation dinitrogen trioxide. Very little oxidation to oxides of carbon occurs, these representing on exit-gas analyses less than 0·1% of the propylene consumed. Addition of oxygen with the propylene gives a product more stable to distillation, much less contaminated with materials arising from addition of trioxide, and richer in nitropropyl nitrate.

*Separation Procedure.*—Ether and excess of tetroxide are removed by careful distillation under reduced pressure. For reasons already stated (Part II), continuous evaporation from a warm, falling film is preferred, with the crude product falling immediately into cold water to convert the β-nitro*iso*propyl nitrite into nitropropanol (see British Patent Application No. 17,160/45). Two washings with water are usually sufficient and, after being neutralised with calcium carbonate, the bulked aqueous layers are extracted continuously with ether to recover β-nitro*iso*propanol, which is purified by a single distillation.

The insoluble oil layer is first dried by azeotropic distillation with benzene. Its composition and subsequent treatment vary according to whether or not oxygen is used in the reaction. When oxygen is added, the insoluble

oil consists of a mixture of roughly equal parts of dinitropropane and nitropropyl nitrate which must be separated by fractional distillation under high vacuum, since the former cannot be obtained by freezing as in the case of dinitro-ethane and -*iso*butane. When oxygen is not added, the insoluble oil contains much less nitropropyl nitrate, but may contain as much as 15—20% of 4-nitro-3-methylfurazan oxide (VIII). Only part of this can be frozen out by dissolving the oil in twice its volume of methanol and cooling to −70°. The oil is then less stable to distillation, and the solid furazan oxide distils over a wide range, interfering with collection of the main product, *viz.*, 1 : 2-dinitropropane.

*Yields.*—The combined yield of distilled β-nitro*iso*propanol and distilled insoluble oil usually accounts for more than 70% of the propylene consumed, but the isolation of pure 1 : 2-dinitropropane, β-nitro*iso*propyl nitrate, and 4-nitro-3-methylfurazan oxide from the insoluble oil occasions some loss, particularly when the last compound is present. Recovery of nitropropanol from the aqueous layer is at best 80%, losses being due to incomplete extraction and to some hydrolytic fission of the nitro-alcohol to nitromethane and acetaldehyde: $CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}NO_2 \longrightarrow CH_3{\cdot}CHO + CH_3{\cdot}NO_2$. Yields of distilled nitropropanol and distilled insoluble oil are given below for reaction with and without oxygen. Corrected figures in parentheses make allowance for experimentally determined extraction and distillation losses.

| | Yields % on propylene consumed. | |
|---|---|---|
| | (*a*) With oxygen. | (*b*) Without oxygen. |
| β-Nitro*iso*propanol ..... | 33·5 (41·9) | 41·3 (51·6) |
| Insoluble oil ..... | 42·0 (42·8) | 31·2 (36·1) |
| Totals ..... | 75·5 (84·7) | 72·5 (87·7) |

In case (*a*), fractional distillation of the insoluble oil gives almost equal molar proportions of 1 : 2-dinitropropane and β-nitro*iso*propyl nitrate, and in case (*b*), freezing, followed by rather troublesome fractional distillation, suggests the following proportions, reduced to yields on propylene consumed: 18—20% of dinitropropane, 3—4% of nitro*iso*propyl nitrate, and 6—8% of 4-nitro-3-methylfurazan oxide. The overall yield on tetroxide consumed is about 94%, and the ether recovery 99%.

These results indicate that types of addition other than the two described do not occur to any considerable extent. Addition to form nitropropyl nitrite appears to be markedly favoured in the case of propylene, while oxygen addition assists its conversion to nitropropyl nitrate. A similar effect with oxygen has been found in the case of *iso*butylene.

*Properties and Reactions of Products.*—*1 : 2-Dinitropropane.* Unlike 1 : 2-dinitro-ethane and -*iso*butane, 1 : 2-dinitropropane has not been obtained as a solid except at low temperatures. This is possibly associated with its asymmetry, the *d*- and the *l*-form being solid, and the *dl*-form liquid at room temperature. The liquid appears to be more stable than 1 : 2-dinitroethane, distilling under high vacuum to give a practically colourless oil, b. p. 88°/*ca.* 1 mm., and developing only a slight yellow tinge in several months' storage Reaction with aqueous alkali, or even weak bases such as urea, gives polymeric 1-nitropropyl-1-ene (see British Patent Application No. 20,484/44): $CH_3{\cdot}CH(NO_2)CH_2{\cdot}NO_2 + NaOH \longrightarrow NaNO_2 + H_2O + CH_3{\cdot}CH{:}CH{\cdot}NO_2 \longrightarrow$ polymer. 1 : 2-Dinitropropane has been further characterised by reduction to 1 : 2-diaminopropane and by acid hydrolysis to hydroxylamine.

*β-Nitroisopropyl nitrite.* β-Nitro*iso*propyl nitrite, prepared from the alcohol by reaction with sodium nitrite and dilute acid, is somewhat more stable than the corresponding nitroethyl nitrite. It can be distilled at 28—30°/< 1 mm., and decomposition with gas evolution on standing is moderately slow. A distilled sample gave N, 20·4 ($C_3H_6O_4N_2$ requires N, 20·9%). Like β-nitroethyl nitrite, it is hydrolysed by water or methyl alcohol to the nitro-alcohol.

β-Nitro*iso*propanol is a colourless mobile liquid, b. p. 68°/*ca.* 1 mm., 106—109°/20 mm., $d_{4^\circ}^{20^\circ}$ 1·192, $n_D^{20^\circ}$ 1·441. It is not affected by storage and is identical with the nitro-alcohol prepared by condensation of nitromethane and acetaldehyde in the presence of basic catalysts. It is oxidised by aqueous dichromate to nitroacetone, and its acetate on heating affords monomeric 1-nitro-1-propylene: $CH_3{\cdot}CH(OAc){\cdot}CH_2{\cdot}NO_2 \longrightarrow CH_3{\cdot}CH{:}CH{\cdot}NO_2 + HOAc$.

β-Nitro*iso*propyl nitrate, when pure, is a colourless mobile liquid, b. p. 71°/*ca.* 1 mm., $d_{4^\circ}^{20^\circ}$ 1·348, $n_D^{20^\circ}$ 1·447. It is a powerful explosive, with approximately 75% of the power of blasting gelatin, and is very insensitive to friction and impact. Reaction with alkali readily abstracts nitric acid to form polymeric nitropropylene (British Patent Application No. 24,764/44), and further characterisation has been provided by comparison with synthetic material, using Wieland and Sakellarios's nitration procedure (*Ber.*, 1920, **53**, 201) for 2-nitroethanol on β-nitro*iso*propanol prepared from nitromethane and acetaldehyde.

4-Nitro-3-methylfurazan oxide is a white solid identical with the substance prepared by Behrend and Schmitz (*Annalen*, 1893, **277**, 310). It crystallises from methanol to give large hexagonal plates, m. p. 67—69°. The melt is stable to heat, no discernible decomposition (*e.g.*, gas evolution) occurring during 40 hours at 100°. The solid dissolves in warm aqueous alkali and has been catalytically reduced in acetic acid with hydrogen at 100 atm. to give *4-amino-3-methylfurazan oxide.*

## Experimental.

*Reagents.*—Pure liquid dinitrogen tetroxide was prepared as described in Part II. Propylene was obtained by dehydrating *iso*propanol over active alumina (" Alorco " chips) at 350—400°. The issuing gases were cooled to condense

water and unchanged *iso*propanol, washed with water, and dried with calcium chloride before passing directly to the nitration vessel or to catch-pots at − 70° for storage as liquid. The alumina catalyst was regenerated at 4-hour intervals by passage of air at 450°, and the purity of the propylene frequently checked by analysis. The ethyl ether used as reaction solvent was washed several times with water to remove any alcohol present, dried over calcium chloride and then metallic sodium, and finally distilled from and stored over sodium.

*Nitration Procedure.*—The apparatus was similar to that described in Part II, and two typical runs are described: (*a*) with oxygen added to the propylene before absorption, (*b*) without oxygen. (*a*) In the first, 48·5 l. of propylene (85 g.) and 23·5 l. of oxygen were passed into a solution of 435 g. of tetroxide in 1003 g. of ether during 3 hours. Absorption was rapid, and the solution retained its pale amber colour. In (*b*), 68·0 l. of propylene (119 g.) were passed into a solution of 615 g. of tetroxide in 1540 g. of ether, also during 3 hours, the solution turning a bright green. The external bath temperature was kept at 0° in both cases. The concentrations of tetroxide in ether (30·2% and 28·5% by weight) and the molar percentage absorption of propylene (42·6% and 42·4%) were similar for the two cases.

*Separation and Purification of Products.*—(a) *With oxygen.* Ether and excess of tetroxide were removed at water-pump pressure and collected for re-use in traps cooled to − 70°. The total weight recovered was 1265 g., compared with 1252 g. calculated from complete reaction of the propylene absorbed. The pale green reaction product remaining weighed 257 g. (Calc.: 271 g.), and was stirred with 4 vols. of water. The oil was separated, and washed successively with 2 vols. and with 1 vol. of water, the three aqueous layers being bulked for continuous extraction with ether. After the ethereal extract had been dried ($Na_2SO_4$), the ether was removed under suction, and the 2-nitro*iso*propanol distilled (71·2 g., 33·5% yield on propylene) (Found: C, 34·1; H, 6·7; N, 13·8. Calc. for $C_3H_7O_3N$: C, 34·3; H, 6·7; N, 13·3%).

The insoluble oil (130 g.) was mixed with an equal volume of methanol and cooled to − 70°, but no solid deposited. Methanol was removed under vacuum, and the residual oil dried by adding 80 ml. of benzene and distilling off the latter with the moisture at about 1 mm. pressure and a bath temperature not exceeding 30°. The remaining oil (123·9 g.) was distilled under high vacuum to give the following fractions: (i) 5·5 g., b. p. 68—79°/1 mm.; (ii) 60·3 g., b. p. 79—86°/1 mm.; (iii) 54·8 g., b. p. 86—92°/1 mm.; residue, 2·1 g. Distillation was smooth throughout and no 4-nitro-3-methylfurazan oxide was obtained. The first two fractions were combined and redistilled to give *β-nitroisopropyl nitrate* (61·7 g.), b. p. 78—80°/1 mm. (Found: C, 25·7; H, 4·5; N, 19·0. $C_3H_6O_5N_2$ requires C, 24·0; H, 4·0; N, 18·7%). Redistillation of fraction (iii) gave 49·7 g. of 1 : 2-*dinitropropane*, b. p. 89—90°/1 mm. (Found: C, 27·3; H, 4·4; N, 20·2. $C_3H_6O_4N_2$ requires C, 26·8; H, 4·5; N, 20·9%). Fractions (i) and (ii) represent a 21·4% yield of nitropropyl nitrate on propylene consumed, and fraction (iii) a 20·2% yield of dinitropropane.

(b) *Without oxygen.* Ether and excess of tetroxide were removed as before, and the crude product stirred with 1400 ml. of water to give 160 ml. of insoluble oil. This was stirred with 320 ml. of water to give 130 ml. of oil which was reduced by further washing with 250 ml. of water to 128 ml. (158 g.). To this was added a further 15 g. of oil which separated from the bulked aqueous layer. The mixture was extracted with ether and treated as before, giving 122·9 g. of 2-nitro*iso*propanol, b. p. 68°/*ca.* 1 mm. (Found: C, 34·1; H, 6·7; N, 13·5. Calc. for $C_3H_7O_3N$: C, 34·3; H, 6·7; N, 13·3%). The yield on propylene consumed was 41·3%, and there remained 29·2 g. of distillation residue.

The 178 g. of insoluble oil were mixed with an equal volume of methanol and cooled to − 70°. Some solid separated, but melted on the filter and passed through. After removal of methanol under suction, the 151 g. of oil remaining were dried by azeotropic distillation with 70 ml. of benzene as above, leaving 148 ml. of oil to be distilled under high vacuum. This gave two fractions: (i) 4·8 g., b. p. 58—86°/3 mm.; (ii) 113·5 g., b. p. 86—108/2 mm.; residue, 18·6 g. Gas evolution during the beginning and end of distillation necessitated occasional chilling of the boiler with a solid carbon dioxide–methanol bath. Distillation of the first fraction and the early part of the second was accompanied by deposition of solid 4-nitro-3-methylfurazan oxide in the receiver. A total of 11·6 g. of this solid was separated from the two fractions by dissolving them in methanol and cooling at − 70° overnight. It was recrystallised from methanol to give large hexagonal plates, m. p. 67—69° (Found: C, 25·2; H, 2·2; N, 29·1; *M*, 145. Calc. for $C_3H_3O_4N_3$: C, 24·8; H, 2·1; N, 29·0%; *M*, 145).

Methanol was removed under suction from the combined filtrates, the oil dried with benzene as before, and fractional distillation repeated to give: (i) 1·9 g., b. p. 61—76°/1·5 mm.; (ii) 15·7 g., b. p. 76—78°/1·5 mm.; (iii) 77·5 g., b. p. 96—104°/1·5 mm.; residue, 1·0 g. Fraction (ii) gave a further 3·4 g. of the furazan oxide on freezing in methanol, and the early fractions from the redistillation of (iii) in an efficient packed still gave 6·5 g. more, together with a final fraction of 55·8 g. of pure 1 : 2-dinitropropane. The final result of this complicated combination of freezing out the solid and fractional distillation was: 21·5 g. of pure 4-nitro-3-methylfurazan oxide (5·2% on propylene consumed), 55·8 g. of pure 1 : 2-dinitropropane (14·8%), and 24·6 g. of oil (approximately 6·5%) remaining after solid was frozen out of various fractions and consisting largely of 1 : 2-dinitropropane with some nitropropyl nitrate and some 4-nitro-3-methylfurazan oxide. Distillation residues totalled another 24 g.

*Preparation of Derivatives.—Reduction of 1 : 2-dinitropropane to propylenediamine.* 0·467 G. of dinitropropane was dissolved in 30 ml. of acetic acid and reduced with electrolytic hydrogen at 85 atm. in the presence of 0·022 g. of Adams's catalyst. The catalyst was then filtered off, the solution saturated with dry hydrogen chloride, and the acetic acid distilled off under reduced pressure, leaving 0·488 g. of crude dihydrochloride (93·5% yield); it was washed with cold alcohol (Found: Cl, 46·6%) and then recrystallised from alcohol, and had m. p. 220—222° (Found: Cl, 47·6. Calc. for $C_3H_{10}N_2,2HCl$: Cl, 48·3%) (lit. m. p. 220°).

The dipicrate had m. p. 237° (lit. 237°) (Found: C, 33·4; H, 3·4; N, 21·3. Calc. for $C_3H_{10}N_2,2C_6H_3O_7N_3$: C, 33·8; H, 3·0; N, 21·1%).

*Acid hydrolysis of 1 : 2-dinitropropane.* Reaction for 15 minutes at 150° of 0·300 g. of the dinitropropane with 4·5 ml. of concentrated hydrochloric acid gave, after dilution with 250 ml. of distilled water, 0·0510 g. of hydroxylamine as determined by the procedure outlined in Part II. The yield was 69·1% based on a single primary nitro-group.

*Oxidation of β-nitroisopropanol to nitroacetone.* A mixture of 24·5 g. of nitropropanol, 37·5 g. of sodium dichromate, and 22·5 ml. of water was vigorously stirred and kept at 20—25° while 45 g. of concentrated sulphuric acid in 11·5 ml. of water were added during 2 hours. After a further 2½ hours' stirring, the mixture was diluted with water and extracted three times with 60 ml. of ether. The ether was removed under reduced pressure, leaving 19·8 g. of white crystalline solid (82·5% yield). Two recrystallisations from methanol gave nitroacetone, m. p. 50—51° (Found: C, 35·8; H, 5·2; N, 14·2. Calc. for $C_3H_5O_3N$: C, 35·0; H, 4·9; N, 13·6%). Henry (*Bull. Acad. roy. Belg.*, 1898, **36**, 149) described nitroacetone as a colourless liquid, b. p. 152°/717 mm., but Harries (*Annalen*, 1901, **319**, 251) obtained it as a white solid, m. p. 50—57°. Its anil, prepared by Harries's method (*loc. cit.*), had m. p. 85—87° after crystallisation from ethyl alcohol (Harries gives m. p. 87°) (Found: C, 60·5; H, 6·1; N, 16·4. Calc. for $C_9H_{10}O_2N_2$: C, 60·7; H, 5·6; N, 15·7%).

Similar results were given with nitroacetone prepared from synthetic β-nitro*iso*propanol (condensation of nitromethane and acetaldehyde). Nitroacetone crystals tend to become yellow and oily on standing for 2—3 weeks but can be purified by recrystallisation from methanol. They are best stored over potassium hydroxide.

*β-Nitroisopropyl acetate and 1-nitropropyl-1-ene.* To 170 g. of acetyl chloride were added 90 g. of nitropropanol at a rate just sufficient to maintain reflux, and the mixture was then refluxed for a further hour. The excess of acetyl chloride

and the acetic acid formed were removed under reduced pressure, and the residue distilled to give 118 g. (94%) of acetate, b. p. 76/*ca.* 1 mm.; this was purified by redistillation (Found: C, 40·5; H, 6·1; N, 10·0. Calc. for $C_5H_9O_4N$: C, 40·9; H, 6·1; N, 9·7%).

The nitro-olefin was prepared from the acetate (50 g.) by heating it with freshly fused and powdered sodium acetate (0·2 g.) at 110—120° for 40 minutes under reflux. The product was then distilled rapidly under 1 mm. pressure into a receiver cooled to − 70°. The lachrymatory oil so obtained was washed four times with saturated sodium chloride solution, dissolved in an equal volume of ether, and dried over calcium chloride. The ether was removed and the oil distilled to give 20·5 g. (78%) of 1-nitropropyl-1-ene, b. p. 37—42°/10 mm., and 6·2 g. of unchanged acetate.

Similar results were obtained in both preparations with 2-nitro*iso*propanol from nitromethane and acetaldehyde.

*Polymeric nitropropylene from β-nitroisopropyl nitrate.* A solution of 0·266 g. of sodium hydroxide in 20 ml. of water was added dropwise (20 mins.) to a stirred solution of 1 g. of nitropropyl nitrate in 10 ml. of methanol. After a further 30 minutes' stirring, the mixture was acidified with dilute hydrochloric acid, and the solid polymer was filtered off, washed with water and methanol, and dried in a vacuum desiccator over calcium chloride and phosphoric oxide; yield, 0·274 g. (42%) of somewhat moist polymer [Found: C, 40·0; H, 5·6; N, 15·4. Calc. for $(C_3H_5O_2N)_n$: C, 41·4; H, 5·75; N, 16·1%].

*Preparation of β-nitroisopropyl nitrate from nitropropanol.* Nitropropanol (230 g., prepared from nitromethane and acetaldehyde) was added slowly with stirring to a mixture of 500 g. of nitric acid (98%) and 1000 g. of concentrated sulphuric acid. The mixture was stirred for a further hour, set aside overnight, and the top layer separated and poured into 2 l. of iced water. The mixture was stirred, and the oil separated for a further washing with 350 ml of water; it was then dried by azeotropic distillation with 180 ml. of benzene to give 202·5 g. (61·8%) of the nitrate, b. p. 76°/< 1 mm. (Found: C, 24·1; H, 4·2; N, 18·6. Calc. for $C_3H_6O_5N_2$: C, 24·0; H, 4·0; N, 18·7%). *4-Amino-3-methylfurazan oxide*, formed by reduction of the nitro-compound as described on p. 1103, is a pale yellow solid, m. p. 175° (Found: C, 31·7; H, 4·7; N, 34·8. $C_3H_5O_2N_3$ requires C, 31·3; H, 4·4; N, 36·5%).

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## 243. *Contributions to the Chemistry of Pyridine. Part I. Condensation of β-Hydroxypyridine with Formaldehyde in Alkaline Medium.*

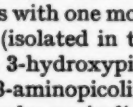
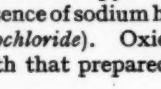
By T. URBAŃSKI.

3-Hydroxypyridine reacts with formaldehyde in the presence of aqueous sodium hydroxide, furnishing *3-hydroxy-2-hydroxymethylpyridine*. The position of the hydroxymethyl group was established by oxidation of the substance to the known 3-hydroxypicolinic acid.

Some derivatives of 3-hydroxy-2-hydroxymethylpyridine have been prepared.

THE fact that 3-hydroxypyridine is related to the vitamin B group (Williams, *J. Ind. Eng. Chem.*, 1921, **13**, 1107; Kuhn *et al.*, *Ber.*, 1939, **72**, 305, 309, 310, 311; Stiller, Keresztesy, and Stevens, *J. Amer. Chem. Soc.*, 1939, **61**, 1237; Harris, Stiller, and Folkers, *ibid.*, p. 1242) creates a new interest in this compound. In an investigation of the possibility of the direct introduction of hydroxymethyl groups into 3-hydroxypyridine by the action of formaldehyde, in order to produce a substance similar to pyridoxine, it has been found that 3-hydroxypyridine condenses with one mol. of formaldehyde in presence of sodium hydroxide, forming *3-hydroxy-2-hydroxymethylpyridine* (I) (isolated in the first place as its *hydrochloride*). Oxidation of this compound with sodium permanganate gives 3-hydroxypicolinic acid, identical with that prepared by Kirpal (*Monatsh.*, 1908, **29**, 231) by diazotisation of 3-aminopicolinic acid.

Attempts to esterify 3-hydroxypicolinic acid with methyl alcohol in presence of hydrochloric or sulphuric acid gave negligible yields. Better results were obtained by the action of methyl alcohol on the acid chloride or the action of methyl iodide on the silver salt of the acid. The same ester (m. p. 72—73°) was obtained by either reaction, whether the acid had been made from 3-aminopicolinic acid or by oxidation of 3-hydroxy-2-hydroxymethylpyridine. For this reason, an alternative structure (II) for the hydroxy-hydroxymethylpyridine should be rejected. This structure was ascribed by Aso (*J. Agric. Chem. Soc. Tokyo*, 1939, **15**, 629; 1940, **16**, 249) to one of the products which he obtained from sugars or ethoxymethylfurfuraldehyde and ammonium salts.

(I.)  (II.) 

Both hydroxyl groups in 3-hydroxy-2-hydroxymethylpyridine can be esterified with acetic anhydride in presence of sodium acetate. Boiling of (I) with 60% hydrobromic acid yields the *hydrobromide* of *3-hydroxy-2-bromomethylpyridine*. This is easily hydrolysed by heating with water and yields the *hydrobromide* of (I).

### EXPERIMENTAL.

*3-Hydroxy-2-hydroxymethylpyridine Hydrochloride.*—3-Hydroxypyridine (0·2 mol., 19 g.) was dissolved in 10% aqueous sodium hydroxide (94 c.c.) and 36% formaldehyde (42 c.c., 0·5 mol.). The solution was refluxed on the water-bath for 1½—2 hours, during which time it acquired a ruby colour. After being cooled, it was acidified with glacial acetic acid (19 c.c.) and evaporated. The syrupy residue was extracted with acetone (*ca.* 2 l.). The colour changed to green or bluish-green. (The changes of the colour, *viz.*, red in alkaline and green or blue in the acid medium, are probably due to formation of coloured open-chain products of the type described by Zincke, *Annalen*, 1904, **330**, 361; 1905, **339**, 193, **341**, 365.) The acetone was distilled off, and alcoholic hydrogen chloride was added to the syrupy residue. Crystalline *3-hydroxy-2-hydroxymethylpyridine hydrochloride* was filtered off and washed with acetone (yield 16·5 g.;

51%) (Found : C, 44·3; H, 5·0; N, 8·6; Cl, 22·4. $C_6H_8O_3NCl$ requires C, 44·5; H, 5·0; N, 8·7; Cl, 22·0%). It was purified by dissolving it in aqueous acetone (100 c.c. acetone + 20 c.c. water) and adding more acetone (*ca.* 1·5 l.). Repeated crystallisation gives needles, m. p. 206°. The substance is readily soluble in water, soluble in alcohol, insoluble in most organic solvents. It gives a yellow colour with ferric chloride.

*3-Hydroxy-2-hydroxymethylpyridine* (I).—(*a*) The hydrochloride of (I) (1 g.) was dissolved in sufficient 10% sodium carbonate solution to give a neutral solution (litmus), the solution evaporated, and the residue extracted with acetone. Evaporation of the acetone left a syrup which crystallised slowly. The crystals were washed with a small quantity of water and crystallised from water (or acetone); m. p. 132° (0·15 g.). As this method leaves sodium salts in the substance, the following method is preferable. (*b*) The hydrochloride of (I) (1 g.) was dissolved in water and acidified with acetic acid. Freshly precipitated silver oxide was added, and silver chloride filtered off. The solution was saturated with hydrogen sulphide, silver sulphide filtered off, and the filtrate evaporated. The syrupy residue crystallised in a desiccator over potassium hydroxide, and was recrystallised from water; m. p. 130° (0·25 g.). The *substance* (Found : C, 57·3; H, 5·3; N, 11·6. $C_6H_7O_2N$ requires C, 57·6; H, 5·6; N, 11·2%) is soluble in water, alcohol, or hot acetone, insoluble in benzene, ether, methyl acetate, or light petroleum.

The *picrate* crystallised from hot water in light yellow needles, m. p. 208—210° (Found : C, 40·4; H, 3·2; N, 15·9. $C_{13}H_{10}O_9N_4$ requires C, 40·7; H, 2·8; N, 15·8%). The methiodide, prepared as a reddish oil soluble in water or alcohol, insoluble in ether and in methyl iodide, was dissolved in small quantity of alcohol and precipitated with ether, and then crystallised slowly in needles, m. p. 140°. The base formed a platinichloride, hygroscopic, reddish-brown needles.

*3-Hydroxy-2-bromomethylpyridine Hydrobromide.*—3-Hydroxy-2-hydroxymethylpyridine hydrochloride (1 g.) was boiled with 60% hydrobromic acid (20 c.c.) for 10 mins. under reflux. The resulting solution was evaporated to *ca.* 10 c.c. and crystallised on cooling. The *hydrobromide* is insoluble in most organic solvents and the bromomethyl group was hydrolysed readily in hot water. It was therefore purified only by washing with small quantity of cold water, acetone, and ether; yield 1·2 g. of needles, m. p. 182—184° (Found : N, 5·1; Br, 60·5. $C_6H_7ONBr_2$ requires N, 5·2; Br, 59·4%). When heated above its m. p., it develops an intense purple colour.

*3-Hydroxy-2-hydroxymethylpyridine Hydrobromide.*—(*a*) A solution of the foregoing hydrobromide (1·2 g.) in water (10 c.c.) was evaporated down to 2—3 c.c. on the water-bath; white prisms of the *hydrobromide* of (I) crystallised on cooling (1·0 g.), m. p. 205—207° (Found : N, 6·7; Br, 39·5. $C_6H_8O_2NBr$ requires N, 6·8; Br, 38·8%). It is soluble in water, relatively soluble in acetone, insoluble in most organic solvents. (*b*) 3-Hydroxy-2-hydroxymethylpyridine (0·2 g.) was dissolved in 25% hydrobromic acid (2 c.c.) and left in a vacuum desiccator over potassium hydroxide. Crystals of the hydrobromide of (I) (0·28 g.) resulted; m. p. and mixed m. p. 204—208°.

*Acetylation of 3-Hydroxy-2-hydroxymethylpyridine.*—The hydrochloride of (I) (2 g.), acetylated in the normal manner, afforded *3-acetoxy-2-acetoxymethylpyridine* as an oil. It was extracted with ether, dried ($Na_2SO_4$), and distilled under reduced pressure. A fraction, b. p. 118—122°/4 mm., was collected (1·5 g.) as a colourless, viscous liquid, appreciably soluble in water; $n_D^{20°}$ 1·4881 (Found : Ac, 41·1. $C_{10}H_{11}O_4N$ requires 2Ac, 41·1%).

*Oxidation of 3-Hydroxy-2-hydroxymethylpyridine.*—The hydrochloride of (I) (3 g.) was dissolved in water (150 c.c.) and 10% sodium carbonate solution (40 c.c.). A solution of sodium permanganate (7·0 g.) in water (150 c.c.) was added gradually with stirring below 5°. The solution was left overnight at room temperature, oxides of manganese filtered off and washed with water, and the filtrate and washings neutralised with 10% sulphuric acid and concentrated to *ca.* 100 c.c. Acidification with acetic acid and addition of copper acetate precipitated the light green cupric salt of 3-hydroxypicolinic acid. This salt was decomposed with hydrogen sulphide in the usual way, and the filtrate evaporated to dryness. The substance still contained sodium salts and was purified by reprecipitation of the cupric salt; yield 1·2—1·6 g. It crystallises from water, acetone, or light petroleum in white needles or plates, m. p. 205°. It is soluble in hot water, or in alcohol, acetone, xylene, or light petroleum. It gives an intense cherry-red colour with ferrous sulphate and a lighter one with ferric chloride (Found : C, 51·5; H, 3·9; N, 9·7; equiv. by titration, 141. Calc. for $C_6H_5O_3N$ : C, 51·8; H, 3·6; N, 10·1%; equiv., 139).

The same acid was prepared from 3-aminopicolinic acid (Suchards, *Ber.*, 1925, **58**, 1727) by diazotisation, decomposition of the diazonium compound, and purification through the copper salt; after recrystallisation from water and from light petroleum, it had m. p. 208° (corr. 216°), and mixed with the acid prepared as above, m. p. 205—208°.

*Methyl 3-Hydroxypicolinate.*—(*a*) Esterification by the Fischer–Speier method afforded the methyl ester, m. p. 65°, in poor yield. (*b*) Conversion of the acid (0·4 g.) into its chloride and thence into the ester afforded white needles (0·03 g.), m. p. 72° after crystallisation from ether. (*c*) Esterification of the acid (0·5 g.) *via* its silver salt and reaction with methyl iodide afforded the *ester* (0·20 g.), m. p. 73° after two crystallisations from ether (Found : C, 54·5; H, 4·6; N, 9·1. $C_7H_7O_3N$ requires C, 54·9; H, 4·6; N, 9·15%). The ester is soluble in alcohol, ether, or chloroform, insoluble in benzene or petroleum. It possesses a characteristic smell of roasted hazel-nuts. It gives a blood-red colour with ferric chloride and a light brown with ferrous sulphate.

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The elementary analyses were done by Drs. G. Weiler and F. E. Strauss, Oxford.

ARMAMENT RESEARCH DEPARTMENT, ROYAL ARSENAL, WOOLWICH. [*Received, January 23rd,* 1946.]

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## 244. *The Nature of the 2-Chloroethyl Chlorovinyl Sulphide Isomers.*

By (the late) R. C. G. MOGGRIDGE.

The decomposition of 1 : 2 : 2′-trichlorodiethyl sulphide [prepared by the chlorination of 2 : 2′-dichlorodiethyl sulphide (" mustard gas ")] gives two compounds which have previously been assumed to be the 2-chloroethyl 1- and 2-chlorovinyl sulphides (I) and (II). They are now believed to be the *cis–trans* isomers of (II), since :

(*a*) A derivative of the aldehyde (III), expected from the hydrolysis of (II), has been obtained from both isomers.

(*b*) By interaction with methylthiol and subsequent oxidation the isomers could be converted to two disulphones, that from (II) having the structure (VI). These disulphones were found to be interconvertible, the " *β* " form giving the " *α* " on treatment with bromine in acetic acid. This behaviour is characteristic of geometrical isomerism, and the disulphones are therefore considered to be the *cis–trans* isomers of (VI).

An attempt to obtain rigid proof of geometrical isomerism by reduction to 2-chloroethyl 2-methylsulphonylethyl sulphone (VII) met with failure.

LAWSON and DAWSON (*J. Amer. Chem. Soc.*, 1927, **49**, 3119) showed that 1 : 2 : 2′-trichlorodiethyl sulphide was formed by the controlled chlorination of 2 : 2′-dichlorodiethyl sulphide ("mustard gas"); this trichloro-compound on being heated decomposed with the elimination of hydrogen chloride. By fractionation they obtained two compounds from the reaction product; these were thought to be the isomeric 2-chloroethyl 1- and 2-chlorovinyl sulphides [" C.E.C.V.S.," (I) and (II)].

$CH_2Cl{\cdot}CH_2{\cdot}S{\cdot}CCl{:}CH_2$ (I.) $CH_2Cl{\cdot}CH_2{\cdot}S{\cdot}CH{:}CHCl$ (II.) $CH_2(OH){\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CHO$ (III.)

Many other workers have since handled these compounds (cf. Lewin and Tschulkow, *J. pr. Chem.*, 1930, **128**, 171; Dawson, *J. Amer. Chem. Soc.*, 1933, **55**, 2070), but the original assumption as to their structure has not been questioned. The compound (II), however, should be capable of geometrical isomerism, and the compounds isolated by Lawson and Dawson might therefore be the *cis–trans* isomers of (II). The isomerism might, in fact, be either structural or geometrical, and none of the work previously published has thrown any light on which of these alternatives is correct. The evidence now presented supports the geometrical nature of the isomerism. It does not exclude the possibility that (I) is also formed, though no evidence of a third isomer has been obtained in this or previous work.

Hydrolysis of (II) would be expected to yield the aldehyde (III); and this compound was in fact isolated by Wadsworth after the hydrolysis of a mixture of the two isomers (private communication). The 2 : 4-*dinitrophenylhydrazone* of this aldehyde has now been isolated from the products of hydrolysis, and its structure has been confirmed by its preparation from the aldehyde (III) which was itself synthesised by the condensation of bromoacetal with the sodium salt of monothioethylene glycol, and hydrolysis of the product.

The isomers, separated by careful fractionation to constant density, were hydrolysed; from each the 2 : 4-dinitrophenylhydrazone of the aldehyde (III) was isolated, the best yields in each case being about 45—50%. Since this compound could hardly arise from (I) it appears that both isomers consisted, at least largely, of (II).

When the isomers were treated with sodium thiomethoxide, the chloroethyl group, as was expected, reacted very much more readily than the chlorovinyl group; the monothioethers so formed could be oxidised to give crystalline *disulphones*. Starting from the mixed isomeric sulphides a mixture of the two disulphones was obtained which could be separated by recrystallisation, while the pure " α " and " β " isomers gave the disulphones, m. p. 180° and 115° respectively, each apparently uncontaminated by the other; this afforded confirmation that the fractionation of the isomeric sulphides had achieved substantial separation of the two components.

These two disulphones could either have the structures (V) and (VI), or, if the sulphides were geometrical isomers, be the *cis–trans* forms of (VI).

(V.) $CH_3{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2{\cdot}CCl{:}CH_2$ $CH_3{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2{\cdot}CH{:}CHCl$ (VI.)

(VII.) $CH_3{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2Cl$ $CH_3{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2{\cdot}CH_2{\cdot}CH_3$ (VIII.)

It was then found that the compound of m. p. 115° could be converted into that of m. p. 180° if it were heated in acetic acid in the presence of a catalyst such as bromine, bromate, or iodate. This phenomenon falls into line with many similar cases of conversion of *cis-* into *trans*-isomers; it is, however, very difficult to explain if the isomerism is structural (V and VI). It is therefore considered probable that the compound of m. p. 115° is the *cis-*, and that of m. p. 180° the *trans-*, isomer of (VI).

If it were possible to reduce the vinyl group of the disulphones without removing the chlorine atom, a rigid proof of the nature of the isomerism should be obtained; the geometrical isomers of (VI) would give the same compound (VII), while (V) would give the corresponding 1-chloroethyl derivative. The compound (VII) was accordingly synthesised by the action of one equivalent of sodium methanesulphinate on 2 : 2′-dichlorodiethyl sulphone (Helfrich and Reid, *J. Amer. Chem. Soc.*, 1920, **42**, 1208). Attempts were then made to reduce the chlorovinyl sulphones catalytically. Unfortunately, no reduction occurred using palladium chloride–gum arabic or platinum–platinum oxide catalysts, and the use of palladised barium sulphate led to the hydrogenation of the double bond and replacement of the chlorine atom. The structure of the 2-*methylsulphonyldiethyl sulphone* (VIII) resulting from the reduction was confirmed by synthesis; ethyl iodide was condensed with the sodium salt of *methyl 2-mercaptoethyl sulphide* (prepared from methyl 2-chloroethyl sulphide), and the product oxidised to the disulphone.

The preparation of (VIII) from the isomeric chlorovinyl disulphones affords general confirmation of their structure; it does not, however, have any bearing on the nature of the isomerism of the sulphides, since (VIII) could be derived from either (V) or (VI). Attempts to prove the structure by reduction were therefore abandoned.

The opportunity is taken to record the preparation of 2-chloroethyl thiolacetate, since it was analogous to the 2-hydroxyethyl thiolacetate expected to be formed on hydrolysis of (I). Neither this compound, nor the diacetate of 2-hydroxyethylthiol, nor the solutions obtained by their hydrolysis, showed any signs of reaction with 2 : 4-dinitrophenylhydrazine.

## Experimental.

**1 : 2 : 2′-*Trichlorodiethyl Sulphide.*—**The following modification of the method of Lawson and Dawson (*loc. cit.*) was normally used. A current of dry air was led over a weighed amount of cooled liquid chlorine, and then into well stirred and cooled 2 : 2′-dichlorodiethyl sulphide (1 mol.) (Gibson and Pope, *J.*, 1920, **117**, 271) without solvent. The rate of chlorine addition was adjusted so that the temperature of the reaction mixture was kept at about 0°. When the addition was finished the mixture was stirred for a further ½ hour at room temperature with an air current; the product was used without further purification for the preparation of the mixed sulphides.

*Chloroethyl Chlorovinyl Sulphides.*—Crude 1 : 2 : 2′-trichlorodiethyl sulphide was kept at 100° for 6 hours in a current of dry air and then distilled. After redistillation through a Widmer column to remove unchanged 2 : 2′-dichlorodiethyl sulphide the material was used as " mixed sulphides ".

The author is indebted to Dr. R. J. Rossner and to Mr. E. Booth for the samples of the pure isomers used in this work. They were prepared by systematic fractionation of " mixed sulphides "; in the second case the fractionation was continued until no further change in density resulted from redistillation.

The properties of the preparations were as follows :—

| | | |
|---|---|---|
| β-Isomer | (*a*) | b. p. 58°/2 mm.; $n_D^{20°}$ 1·5493; $d_4^{20°}$ 1·3220 |
| | (*b*) | b. p. 79—81°/6·5 mm.; $d_4^{20°}$ 1·3222 |
| α-Isomer | (*a*) | b. p. 54°/2 mm.; $n_D^{20°}$ 1·5486; $d_4^{20°}$ 1·3031 |
| | (*b*) | b. p. 69—73·5°/6·5 mm.; $d_4^{20°}$ 1·3015. |

*The* **2 : 4-*Dinitrophenylhydrazone of 2-Hydroxyethylthioacetaldehyde*** (III).—(a) *Isolation experiments.* Samples of the α- or β-isomer (0·3 to 0·5 g.) and water (100 parts) were refluxed for various times; the mixture became homogeneous after about ½ hour. At the end of the hydrolysis the solutions were added to 2 : 4-dinitrophenylhydrazine (1 equiv.) in cold 2N-hydrochloric acid, and the mixtures kept overnight. The *product* was deposited as long needles, and after recrystallisation from aqueous alcohol or from ethyl acetate–petrol melted at 78·5° (Found : C, 40·7; H, 4·3; N, 18·2; S, 10·34. $C_{10}H_{12}O_5N_4S$ requires C, 40·0; H, 4·0; N, 18·7; S, 10·66%). The yields after varying periods of hydrolysis were as follows :

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| β-Isomer | 6 | hours | hydrolysis, | 51% | yield of | product, | m. p. 78° |
| | 18 | ,, | ,, | 45% | ,, | ,, | ,, 75° |
| α-Isomer | 6 | ,, | ,, | 4% | ,, | ,, | ,, 73° |
| | 12 | ,, | ,, | 41% | ,, | ,, | ,, 75° |
| | 18 | ,, | ,, | 45% | ,, | ,, | ,, 74° |

(b) *Synthesis.* Bromoacetal (Freunder and Ladra, *Compt. rend.*, 1905, **140**, 794) (27·5 g.) was added gradually to a warm solution of 2-hydroxyethylthiol (11 g.; cf. Bennett, *J.*, 1921, 423) in sodium ethoxide solution (from 3·1 g. of sodium and 50 c.c. of alcohol). Sodium bromide was rapidly precipitated; the reaction was completed by refluxing for 1 hour, and the mixture was then cooled, acidified with dilute hydrochloric acid, and extracted with chloroform. Concentration of the extracts gave a brown oily residue which appeared to decompose on distillation and was therefore, without further purification, hydrolysed by being kept for 24 hours with hydrochloric acid (600 c.c., 2·5%). The solution was then neutralised by addition of magnesium carbonate, and sodium chloride added. Repeated ether extraction followed by concentration gave the required aldehyde as a partially crystalline mass, which was purified by recrystallisation from petrol; m. p. 56°. The *p*-nitrophenylhydrazone formed needles, m. p. 126° (Wadsworth, *loc. cit.*, records for the aldehyde as isolated from the hydrolysis of the mixed sulphides, m. p. 56·5°; *p*-nitrophenylhydrazone, m. p. 124—125°); the 2 : 4-dinitrophenylhydrazone had m. p. 78°, identical by mixed m. p. with samples prepared as above from the α- and β-isomers.

**2-*Methylsulphonylethyl 2-Chlorovinyl Sulphones.*—**(1) *Preparation.* (*a*) The α-sulphide (1·57 g.) was refluxed for ½ hour with an alcoholic solution of sodium thiomethoxide (12 c.c., 2N, made by distilling methylthiol (*Org. Synth.*, Coll. Vol. **2**, 346) into the equivalent amount of sodium ethoxide solution). The mixture was allowed to cool, dilute acid and chloroform were added, and the chloroform layer was separated, dried, and evaporated to dryness under reduced pressure. The residue, without further purification, was treated with glacial acetic acid (15 c.c.) and hydrogen peroxide (15 c.c., 100 vol.) and heated at 100° for 1 hour. The *α-disulphone* was deposited on cooling in a yield (crude) of about 70%; it could be recrystallised from a mixture of equal volumes of water and glacial acetic acid, from which it was obtained sometimes as needles, sometimes as plates; both melted at 180°, as did a mixture of the two, and interconversion of the two was frequently observed during recrystallisation (Found : C, 26·0; H, 4·3; Cl, 15·5; S, 27·8. $C_5H_9O_4ClS_2$ requires C, 25·8; H, 3·9; Cl, 15·25; S, 27·5%).

(*b*) The β-sulphide was treated with sodium thiomethoxide exactly as above, and the crude product oxidised as before. The resulting *β-disulphone* was deposited in yield (crude) of 60%, and after recrystallisation from alcohol was obtained as mixed needles and plates, m. p. 111° (Found : C, 26·1; H, 4·2; Cl, 14·7%). Repeated recrystallisation from ethyl acetate–petrol gave plates, m. p. 115°, while on heating in a sealed tube to 120° for 1 hour the compound was obtained as needles, m. p. 107°. The mixture of the two melted at 111°, and either, on recrystallisation from alcohol, gave mixed needles and plates.

In both these preparations concentration of the mother liquor gave small crops of the disulphones contaminated with oily products; in neither was any sign of the isomeric disulphone observed.

(*c*) The mixed sulphides on treatment as above gave a mixture of the two disulphones which could be separated by recrystallisation from aqueous acetic acid, the compound of m. p. 115° being considerably more soluble than that of m. p. 180°. In a typical experiment the sulphides (19·5 g.) was refluxed for ½ hour with sodium thiomethoxide (2·5N, 53 c.c.) and the product isolated as above and distilled to give the mixed thioethers (15·2 g.), b. p. 95—105°/3 mm., or, on redistillation, 93—98°/3 mm. This material (2 g.) was treated with glacial acetic acid (15 c.c.) and hydrogen peroxide (15 c.c., 100 vol.) and kept at room temperature for 48 hours. The α-disulphone was deposited and collected; 0·665 g., m. p. 178°. The mother liquors were evaporated to dryness and the residue recrystallised from aqueous acetic acid; the product (0·1 g., m. p. 140—155°) was discarded, while the mother liquors were again concentrated to dryness and recrystallised, this time from alcohol, to give the β-disulphone; 1·2 g., m. p. 107°.

(2) *Interconversion.* The β-disulphone, m. p. 115°, was heated to 100° for 1 hour in a sealed tube with acetic acid containing a trace of bromine. On cooling a solid, m. p. 176°, was deposited; after recrystallisation from aqueous acetic acid it had m. p. 180° and was shown by mixed m. p. to be identical with the α-disulphone prepared as above; yield, almost theoretical. This conversion was also observed if bromine were replaced by potassium bromate or iodate; the compound m. p. 115° was recovered unchanged, however, if heated with acetic acid alone, or with acetic acid and traces of chlorine, iodine, hydrogen chloride, phosphorus pentachloride, or sulphuryl chloride. This conversion could,

if so desired, be applied to the preparation of the disulphone, m. p. 180°, from the mixed sulphides, the reaction mixture from the peracetic acid oxidation being sealed up with a trace of bromine and heated to 100° for 1 hour. The overall yield of pure α-disulphone obtained by this method was 54%.

(3) *Attempted reduction.* The α-disulphone, m. p. 180°, was used for the following experiments:

(*a*) Palladous chloride (1 g.) (cf. Skita *et al.*, *Ber.*, 1909, **42**, 1627; 1912, **45**, 3312, 3579; 1915, **48**, 1486) was dissolved in dilute hydrochloric acid (100 c.c.). The disulphone (0·5 g.) in glacial acetic acid (63 c.c.), dilute hydrochloric acid (7 c.c.), the palladous chloride solution (1 c.c.), and gum arabic (1% solution in water, 2 c.c.) were shaken in an atmosphere of hydrogen for 5 hours at room temperature. The disulphone was recovered unchanged, both in this and in another experiment in which the amount of catalyst was increased tenfold.

(*b*) The platinum–platinum oxide catalyst (*Org. Synth.*, Coll. Vol. **1**, 463) was tried both in alcohol and in acetic acid containing hydrochloric acid; in both cases the disulphone was recovered unchanged.

(*c*) Palladised barium sulphate was prepared by the formaldehyde reduction of palladous chloride in presence of barium sulphate (cf. Schmidt, *Ber.*, 1919, **52**, 409). The disulphone (0·5 g.) in glacial acetic acid (63 c.c.) and dilute hydrochloric acid (7 c.c.) was shaken with the catalyst (0·5 g.) in an atmosphere of hydrogen for 4 hours. The product was recrystallised from aqueous acetic acid; needles m. p. 120°, identical by mixed m. p. with the 2-methylsulphonyldiethyl sulphone prepared as below.

*Methyl 2-Mercaptoethyl Sulphide.*—Sodium (5·5 g.) was dissolved in alcohol (200 c.c.) and the solution saturated with hydrogen sulphide. Methyl 2-chlorethyl sulphide (*Org. Synth.*, Coll. Vol. **2**, 345) (26·5 g.) was now added, and the solution heated to 50° for 30 minutes, and then refluxed for a further 30 minutes. Sodium chloride was removed by filtration, and the filtrate concentrated under reduced pressure. Distillation of the residue gave both the required *thiol* (8 g., b. p. 75—77°/30 mm.) and 2 : 2′-dimethylthiodiethyl sulphide (11 g., cf. Meade and Moggridge, *J.*, 1946, 813). Difficulty was found in getting satisfactory analyses for thiol (Found: SH, 28·0. $C_3H_8S_2$ requires SH, 30·5%); it was, however, satisfactorily characterised by conversion into its *α-naphthylcarbamate*, needles from ethyl acetate–petrol, m. p. 119° (Found: C, 61·5; H, 5·6; N, 5·0; S, 23·3. $C_{14}H_{15}ONS_2$ requires C, 60·7; H, 5·5; N, 5·05; S, 23·1%).

*2-Methylsulphonyldiethyl Sulphone.*—Methyl 2-mercaptoethyl sulphide was added to sodium ethoxide (1 equiv.) in alcohol and the mixture refluxed with ethyl iodide (1 equiv.) for 1 hour. The mixture was then shaken with water and chloroform and the chloroform layer separated, dried, and concentrated; the residue was oxidised by heating at 100° for 1 hour with excess of peracetic acid. The required *disulphone* was deposited on cooling as needles, m. p. 120° (Found: S, 32·2. $C_5H_{12}O_4S_3$ requires S, 32·0%).

*2-Chloroethyl 2-Methylsulphonylethyl Sulphone.*—Solutions of 2 : 2′-dichlorodiethyl sulphone (Helfrich and Reid, *loc. cit.*) and sodium methanesulphinate (1 equiv.; cf. Boeseken and Ockenberg. *Rec. Trav. chim.*, 1914, **33**, 317) in 80% alcohol were mixed and kept at room temperature for 2 hours. The solution was then concentrated under reduced pressure, and the residue recrystallised (with filtration in the hot) from water; the *product* was deposited in 40% yield as needles, m. p. 162° (Found: Cl, 15·2; S, 26·9. $C_5H_{11}O_4ClS_2$ requires Cl, 15·15; S, 27·3%). On being warmed with pure pyridine this compound gave an insoluble quaternary salt, which was collected, washed with ether, and recrystallised from aqueous alcohol. This *compound* was not deliquescent, though it was readily soluble in water to give a solution containing free chloride ions; on being warmed with alkali it decomposed with liberation of pyridine. Yield, 85—90%; m. p. 242° (decomp.) (Found: Cl′, 11·3; S, 20·9. $C_{10}H_{16}O_4NClS_2$ requires Cl′, 11·3; S, 20·4%).

*2-Chloroethyl Thiolacetate.*—To ethylene sulphide (Canadian patent 392,681; B.P. 465,662; also Meade, private communication) (18 g.) in chloroform (100 c.c.) was added redistilled acetyl chloride (26·5 g.), and the mixture was refluxed for ½ hour. The solvent was then removed under reduced pressure and the residue distilled to give the desired *product* in 82% yield, b. p. 54°/4 mm., 62°/7·5 mm. (Found: Cl, 25·7; S, 23·2. $C_4H_7OClS$ requires Cl, 25·65; S, 23·15%).

*2-Acetoxyethyl Thiolacetate.*—2-Hydroxyethylthiol (40 g.) in benzene (100 c.c.) was treated with freshly distilled acetyl chloride; hydrogen chloride was evolved in the cold. The mixture was refluxed for 1 hour and then concentrated under reduced pressure. The residue on distillation gave the required product in almost theoretical yield; b. p. 80—82°/4 mm. (Rojahn and Lemme, *Arch. Pharm.*, 1925, **263**, 612, give b. p. 118—120°/25 mm.) (Found: S, 19·6. Calc. for $C_6H_{10}O_3S$: S, 19·75%).

Neither this nor the previous compound showed any sign of reaction with 2 : 4-dinitrophenylhydrazine, nor did the solutions obtained after refluxing them with water (1 and 5 hours), sodium bicarbonate solution (½ hour), or dilute hydrochloric acid (½ hour).

The author wishes to thank Mr. R. Gaze for his assistance in the catalytic reduction experiments, and Mr. R. J. Charnock for his assistance in much of the rest of this work. He also wishes to thank the Chief Scientific Officer, Ministry of Supply, for permission to publish this work.

RESEARCH ESTABLISHMENT, SUTTON OAK. [*Received, March 12th*, 1946.]

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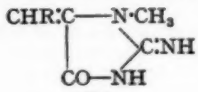
## 245. *Condensation of Substituted Benzaldehydes with Creatinine: Influence of Substituents.*

By VENANCIO DEULOFEU and MANUEL FONDOVILA.

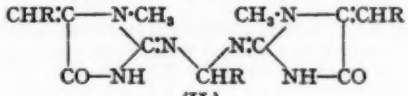
Usually, condensation of substituted benzaldehydes with creatinine by heating at 140° gives derivatives of 5-benzylidenecreatinine (I) and at 190° derivatives of benzylidene-*NN*′-bis-(5-benzylidenecreatinine) (II) are obtained. The fact that *m*-chlorobenzaldehyde gave even at 140° the compound of type (II) while *o*-chlorobenzaldehyde behaved normally, led us to study the influence of substituents. It has been found that *p*-chloro-, *m*-bromo-, *m*-iodo, and *m*-nitro-benzaldehydes condense normally, whereas *p*-nitrobenzaldehyde gives even at 140° a mixture of both types of compound (I) and (II).

THE condensation of creatinine with aromatic aldehydes by fusion was carried out first by Richardson, Welch, and Calvert (*J. Amer. Chem. Soc.*, 1929, **51**, 3075); later, Cornthwaite and Jordan (*ibid.*, 1934, **56**, 2733) effected condensation by heating the two reactants at 130—140°, and Cornthwaite, Lazarus, Snelling, and Denoon (*ibid.*, 1936, **58**, 628) described the condensation of a series of substituted benzaldehydes by heating them with creatinine from 150° to 180° until the reaction ceased. They found that some aldehydes produced two series

of compounds : the usual 5-benzylidenecreatinine derivatives (I) and also a compound formed by condensation of 3 mols. of aldehyde with 2 mols. of creatinine to which the general formula (II) was assigned.



(I.)



(II.)

The constitution of the latter compounds was confirmed by Cattaneo, Deulofeu, and Guerrero (*Ber.*, 1939, **72**, 1461) in the case of benzylidene-*NN'*-bis-(5-benzylidenecreatinine), for hydrolysis with aqueous baryta gave ammonia, benzaldehyde, and 5-benzylidene-1-methylhydantoin, all explicable on the basis of formula (II). They also noted that when the substituted benzaldehydes were heated with creatinine at 140°, only compounds of type (I) could be isolated, whereas heating at 190° afforded compounds of type (II). An exception was *m*-chlorobenzaldehyde, which even at 140° gave only the compound of type (II), the *o*-chlorobenzaldehyde behaving normally. It was therefore considered of interest to study the behaviour of other halogenated benzaldehydes and of the nitrobenzaldehydes, the nitro-group being in some aspects of the opposite type to the halogens.

The halogenated aldehydes employed were *p*-chloro-, *m*-bromo-, and *m*-iodo-benzaldehyde. At 140° all gave only the substituted 5-benzylidenecreatinine (I). The structure of these compounds was ascertained by acetylation to their 2-*acetyl* derivatives, identical with those obtained by direct condensation of the aldehydes with creatinine under the influence of acetic anhydride. As a further confirmation, the original 2-acetyl-5-benzylidenecreatinines were deacetylated with hydrochloric acid and found to be identical with the compounds obtained by fusion.

When the halogenated aldehydes were heated with creatinine at 190°, compounds of formula (II) were practically the only ones that could be isolated.

Of the three isomeric nitrobenzaldehydes, no definite compounds could be isolated from the condensation of *o*-nitrobenzaldehyde with creatinine at 140° or at 190°. *m*-Nitrobenzaldehyde gave at 140° the product of type (I), and at 190° that of type (II), but *p*-nitrobenzaldehyde yielded at 140° a mixture of the two types of compound, type (I) predominating, thus being similar in reactivity, at low temperature, to *m*-chlorobenzaldehyde.

It is difficult to explain the difference of reactivity of the aldehydes in terms of the inductive or tautomeric effects of the substituents until more data are available.

## Experimental.

M. p.s are not corrected. Although not specifically stated, mixed m. p.s were determined with all pairs of identical compounds obtained by different methods. Acetylation was always carried out on the substituted 5-benzylidenecreatinines obtained by fusion at 140°. The time of heating creatinine with the aldehydes at 140° or 190° was 30 minutes.

2-*Acetyl*-5-p-*chlorobenzylidenecreatinine*.—(*a*) 1 G. of creatinine, 0·5 g. of *p*-chlorobenzaldehyde, 1 g. of fused sodium acetate, and 4 c.c. of acetic anhydride were heated in an oil-bath at 140°. Water was then added, and the precipitated solid filtered off, well washed with water, and recrystallised from ethanol; yellow plates, m. p. 199—201°. (*b*) 0·1 G. of 5-*p*-chlorobenzylidenecreatinine, m. p. 261—263°, was acetylated with acetic anhydride–fused sodium acetate in the usual way, affording yellow plates, m. p. 199—201°, after purification (Found : N, 15·45. $C_{13}H_{11}O_2N_3Cl$ requires N, 15·1%).

5-p-*Chlorobenzylidenecreatinine*.—(*a*) 0·2 G. of the foregoing *acetyl* compound was heated for 5 minutes with 5 c.c. of 2N-hydrochloric acid. The solution was cooled, and a small excess of ammonia added. The precipitate was filtered off, washed with water, and recrystallised from ethanol; yellow needles, m. p. 262—263°. (*b*) 1 G. of creatinine (2 mols.) and 1·68 g. of aldehyde (3 mols.) were heated at 140°. The *product*, washed with cold ethanol and warm water, had m. p. 253°; on recrystallisation from ethanol, yellow needles, m. p. 261—263°, were obtained (Found : N, 17·6. $C_{11}H_{10}ON_3Cl$ requires N, 17·8%).

p-*Chlorobenzylidene*-NN'-*bis*-(5-p-*chlorobenzylidenecreatinine*).—1 G. of creatinine and 1·68 g. of *p*-chlorobenzaldehyde were heated at 190°. The solid *product* was washed with warm water and warm ethanol, and the residue recrystallised from acetic acid or nitrobenzene. In both cases yellow-orange needles, m. p. 315—316° (Found : N, 14·5. $C_{23}H_{23}O_2N_6Cl_3$ requires N, 14·2%), were obtained.

2-*Acetyl*-5-m-*bromobenzylidenecreatinine*.—The *m*-bromobenzaldehyde was prepared from *m*-aminobenzaldehyde (Buck and Ide, *Org. Synth.*, Coll. Vol. II, p. 132) with the necessary precautions to avoid production of *m*-chlorobenzaldehyde. (*a*) 0·5 G. of creatinine and 1·2 g. of *m*-bromobenzaldehyde were condensed in the usual way with acetic anhydride–fused sodium acetate. Recrystallisation from ethanol gave yellow needles, m. p. 160—161°. (*b*) Acetylation of 5-*m*-bromobenzylidenecreatinine gave the same compound, m. p. 161° (Found : N, 12·45. $C_{13}H_{12}O_2N_3Br$ requires N, 12·4%).

5-m-*Bromobenzylidenecreatinine*.—(a) By deacetylation of the above *acetyl* compound with 2N-hydrochloric acid, slight yellow plates, m. p. 251—252°, were obtained from ethanol. (*b*) 0·5 G. (2 mols.) of creatinine and 1·1 g. (3 mols.) of aldehyde were heated at 140°. The *product*, washed with cold ethanol, warm water, and warm ethanol, had m. p. 249°, and recrystallised from ethanol, m. p. 249—250° (Found : N, 14·7. $C_{11}H_{10}ON_3Br$ requires N, 15·0%).

m-*Bromobenzylidene*-NN'-*bis*-(5-m-*bromobenzylidenecreatinine*).—0·5 G. of creatinine and 1·1 g. of aldehyde were heated at 190°. The *product* was washed with ethanol, water, and again ethanol, and crystallised twice from aniline and twice from nitrobenzene; yellow needles, m. p. 296—298° (Found : N, 11·4. $C_{23}H_{23}O_2N_6Br_3$ requires N, 11·6%).

2-*Acetyl*-5-m-*iodobenzylidenecreatinine*.—The *m*-iodobenzaldehyde was prepared according to Patterson (*J.*, 1896, **69**, 1002); m. p. 57°. (*a*) 0·5 G. of creatinine and 0·5 g. of *m*-iodobenzaldehyde were condensed in the usual way; yellow plates, m. p. 192°, were obtained from ethanol. (*b*) Acetylation of 5-*m*-iodobenzylidenecreatinine gave the same *compound*, m. p. 190—192° (Found : N, 11·4. $C_{13}H_{12}O_2N_3I$ requires N, 11·4%).

5-m-*Iodobenzylidenecreatinine*.—(*a*) By deacetylation of the foregoing compound with 6N-hydrochloric acid, slight

yellow needles, m. p. 241—242° (from alcohol), were obtained. (*b*) By heating 0·5 g. (2 mols.) of creatinine and 1·4 g. (3 mols.) of aldehyde to 140°, and washing the product with warm water and warm ethanol, this *compound* was obtained, m. p. 233—235°. After recrystallisation from ethanol, it had m. p. 241—243° (Found: N, 12·2. $C_{11}H_{10}ON_3I$ requires N, 12·8%).

m-*Iodobenzylidene*-NN′-*bis*-(5-m-*iodobenzylidenecreatinine*).—0·5 G. of creatinine and 1·4 g. of aldehyde were heated to 190°. The crude *product* was washed with warm ethanol and warm acetic acid. Recrystallised from nitrobenzene, it formed bright yellow needles, m. p. 317—319° (Found: N, 10·5. $C_{29}H_{23}O_2N_6I_3$ requires N, 11·2%).

2-*Acetyl*-5-o-*nitrobenzylidenecreatinine*.—2 G. of creatinine and 1 g. of *o*-nitrobenzaldehyde were condensed as usual with acetic anhydride. The crude *product*, recrystallised from ethanol or acetic acid, gave long yellow needles, m. p. 228—230° (Found: N, 19·3. $C_{13}H_{13}O_4N_4$ requires N, 19·4%). By deacetylation with 2N-hydrochloric acid, 5-o-*nitrobenzylidenecreatinine*, yellow needles, m. p. 250—252°, was obtained from ethanol or acetic acid (Found: N, 23·3. $C_{11}H_{10}O_3N_4$ requires N, 22·8%). By acetylation, the original substance, m. p. 228—230°, was produced.

2-*Acetyl*-5-m-*nitrobenzylidenecreatinine*.—(*a*) 1 G. of creatinine and 0·5 g. of aldehyde were condensed with acetic anhydride. The *acetyl* compound, washed with warm water and ethanol, and recrystallised from nitrobenzene, afforded yellow needles, m. p. 263—264°. (*b*) Acetylation of 5-*m*-nitrobenzylidenecreatinine (below) gave the same product, m. p. 261° (Found: N, 19·9%).

5-m-*Nitrobenzylidenecreatinine*.—(*a*) By deacetylation of the above acetyl compound with 6N-hydrochloric acid, and recrystallisation of the crude product from acetic acid, yellow crystals, m. p. 315° (darkening from 285°) were obtained. (*b*) 0·5 G. (2 mols.) of creatinine and 0·9 g. (3 mols.) of the aldehyde were heated to 140°. The crude product, washed with water and ethanol, had m. p. 285—288°. Recrystallisation from acetic acid afforded yellow needles, m. p. 315° (darkening from 285—288°) (Found: N, 22·5. Calc. for $C_{11}H_{10}O_3N_4$: N, 22·8%). Richardson *et al.* (*loc. cit.*) give m. p. 288°.

m-*Nitrobenzylidene*-NN′-*bis*-(5-m-*nitrobenzylidenecreatinine*).—1 G. of creatinine (2 mols.) and 2 g. of aldehyde (3·6 mols.) were heated to 190°. The crude *product*, washed with warm water and ethanol and recrystallised from nitrobenzene, formed long yellow needles, m. p. 342—344° (Found: N, 20·4. $C_{29}H_{23}O_8N_9$ requires N, 20·15%).

2-*Acetyl*-5-p-*nitrobenzylidenecreatinine*.—(*a*) 1 G. of creatinine and 0·5 g. of the aldehyde were condensed. The crude *product*, after recrystallisation from acetic acid, was obtained as long yellow needles, m. p. 243—244°. (*b*) Acetylation of 5-*p*-nitrobenzylidenecreatinine gave the same substance, m. p. 240° (Found: N, 20·04%).

5-p-*Nitrobenzylidenecreatinine*.—(*a*) By deacetylation of the acetyl derivative with 6N-hydrochloric acid, and recrystallisation from acetic acid, this *nitro*-compound was obtained as yellow prisms, m. p. 284°. (*b*) 1 G. of creatinine and 1·8 g. of the aldehyde were heated at 140°. The crude product, washed with ethanol, warm water and warm ethanol, afforded 0·97 g., m. p. 265°. By boiling with acetic acid soluble and an insoluble fraction (0·16 g.) were separated. By cooling and partial evaporation, the acetic acid solution yielded 0·6 g. of yellow prisms, m. p. 272—275°, raised by recrystallisation from the same solvent to 282—284° (Found: N, 22·0%). The insoluble fraction after recrystallisation from nitrobenzene yielded the *compound* of type (II), m. p. 338—340° (see below).

p-*Nitrobenzylidene*-NN′-*bis*-(5-p-*nitrobenzylidenecreatinine*).—1 G. of creatinine and 1·8 g. of the aldehyde were heated to 190°. The crude product was washed with the usual solvents and extracted with boiling acetic acid but no 5-*p*-nitrobenzylidenecreatinine could be isolated. Recrystallisation from nitrobenzene afforded red needles, m. p. 338—340° (Found: N, 21·0%).

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## 246. *Molecular Compound Formation in the Polyphenyl Series. Part I. Some Compounds formed by 4 : 4′-Dinitrodiphenyl.*

By W. S. RAPSON, D. H. SAUNDER, and E. THEAL STEWART.

Molecular compounds of 4 : 4′-dinitrodiphenyl with various diphenyl derivatives are described. It is demonstrated from their chemical compositions and from their crystal structures (to be described in detail elsewhere) that the molecular ratios in which the components of these compounds unite are determined almost exclusively by geometrical considerations. Interaction of dipoles and not an ionization process is visualized as the basis of compound formation in this series.

THE formation of deeply coloured molecular compounds from quinones and nitro-compounds on the one hand and certain unsaturated hydrocarbons and their derivatives on the other has been attributed (Weiss, *J.*, 1942, 245) " to a complex molecule, essentially ionic in character, which is formed from the two components by an electron transfer from the unsaturated hydrocarbon or its derivative (donor A) to the polynitro-compound (acceptor B) according to the net reaction $A + B \rightleftarrows [A]^+ [B]^-$." This postulate of an integral electron transfer from A to B can be regarded, however, as possibly valid only in limiting cases " where deep coloration accompanies molecular compound formation, and where the presence of ions or ion pairs is supported by other evidence " (*idem, J.*, 1943, 463). The very great variations in colour and stability encountered in these molecular compounds suggest that in most cases interaction of dipoles, leading perhaps to an incipient oxidation–reduction reaction (Hammick and Yule, *J.*, 1940, 1539; Gibson and Loeffler, *J. Amer. Chem. Soc.*, 1940, **62**, 1324) is the more probable basis of compound formation.

The union of the components in simple stoicheiometric ratio (usually 1 : 1, though sometimes 2 : 1) has provided strong support for the former hypothesis of integral electron transfer as the basis of compound formation; for in the comparatively few cases where a molecular ratio of 2 : 1 has been observed in the past (cf. Kuhn and Winterstein, *Helv. Chim. Acta*, 1928, **11**, 144; Hammick and Sixsmith, *J.*, 1939, 972) the molecule of at least one of the components has contained two groupings capable of resonating separately, and therefore of acting separately as donor or acceptor units. Less simple ratios than these occur, however, and are difficult to explain in terms of any process of integral electron transfer. Thus Hertel and Römer (*Z. physikal. Chem.*, 1930, *B*, **11**, 84) have reported that *s*-trinitrobenzene and fluorene combine in the molecular ratio of 4 : 3. Of

even greater complexity, however, are the molecular compounds of 4 : 4′-dinitrodiphenyl with various diphenyl derivatives described below and listed in Table I.

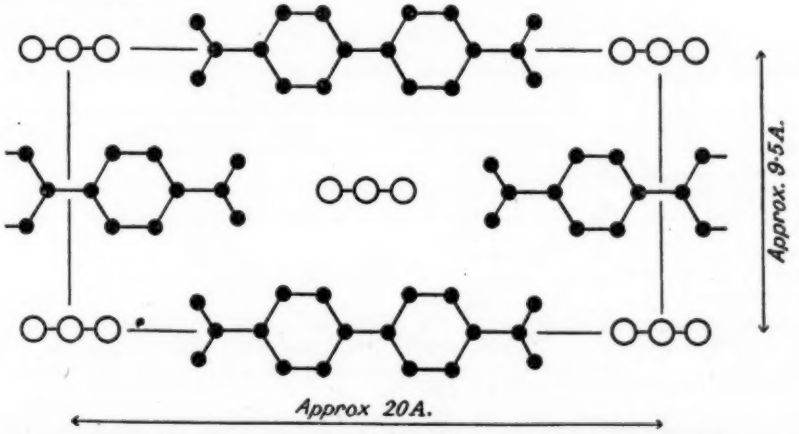
TABLE I.

*Molecular Compounds of* 4 : 4′-*Dinitrodiphenyl.*

| "Donor" component. | Colour. | M. p. | *d.* | *l.* | *n.* | Mol. ratio of components. |
|---|---|---|---|---|---|---|
| 4 : 4′-Diacetoxydiphenyl | Cream | 224—226° | — | 17—18 | 4·6—4·9 | 5 : 1 |
| 4-Acetoxydiphenyl | Cream | 191—221 | — | 14·0—14·5 | 3·8—3·9 | 4 : 1 |
| *NNN′N′*-Tetramethylbenzidine | Dark red | 233 | 1·42 | 15·3 | 4·1 | 4 : 1 |
| | Steel-grey | 224 | — | — | — | 1 : 1 |
| Benzidine | Red | 240 | 1·44 | 13·9 | 3·8 | 4 : 1 |
| 4 : 4′-Dimethoxydiphenyl | Canary-yellow | 216—218 | — | 14·8—15·3 | 4·0—4·1 | 3·5 : 1 |
| 4-Iododiphenyl | Pale yellow | 192—220 | 1·56 | 13·1 | 3·5 | 3·5 : 1 |
| 4-Bromodiphenyl | Cream | 192—220 | 1·52 | 12·8 | 3·5 | 3·5 : 1 |
| 4 : 4′-Dihydroxydiphenyl | Orange-yellow | 249—250 | 1·45 | 12·5 | 3·4 | 3 : 1 |
| 4-Aminodiphenyl | Orange | 220 | — | 12·2 | 3·3 | 3 : 1 |
| 4-Hydroxydiphenyl | Yellow | 228—230 | 1·43 | 11·9 | 3·2 | 3 : 1 |
| Diphenyl | Cream | 191—221 | — | 10·7 | 2·9 | 3 : 1 |

*l* = Approximate length (A.) of "donor" molecule (allowing for approach of next molecule in end-on position).
*n* = Number of molecules of 4 : 4′-dinitrodiphenyl separated by 3·7 A. that can be accommodated at right angles to each "donor" molecule.

4 : 4′-Dinitrodiphenyl has been found to exhibit great selectivity in the formation of molecular complexes, which have been isolated only with 4-substituted and 4 : 4′-disubstituted diphenyls. Diphenyl derivatives with strong electron-donating substituents such as $-NH_2$ or $-OH$ in one or both of the *ortho* positions have failed even to generate colour on admixture with 4 : 4′-dinitrodiphenyl in solution. No evidence has been obtained of compound formation between 2 : 2′-dinitrodiphenyl and any of a large number of simple diphenyl derivatives which have been applied to it.




*Idealized type of structure for the complexes of* 4 : 4′-*dinitrodiphenyl.*

*Each molecule of* 4 : 4′-*dinitrodiphenyl, denoted by black circles, should be seen as several molecules, one above the other, separated by* 3·7 A. *The larger plain circles represent the diphenyl nucleus of the "donor" component seen end-on.*

The compounds of 4 : 4′-dinitrodiphenyl with benzidine and its tetramethyl derivative appear to be by far the most stable of those studied. They are much more intensely coloured (Table I) than those with 4-amino-, 4 : 4′-dihydroxy-, 4-hydroxy-, and 4 : 4′-dimethoxy-diphenyl. These in turn are much more deeply coloured than the remaining complexes listed, all of which have approximately the same colours as the substances from which they are derived. Almost all of these lightly coloured complexes melt with decomposition (over approximately the same range of temperature), indicating that they are less stable than their more deeply coloured analogues. In the cases studied, no complex formation has been observed between 4 : 4′-dinitrodiphenyl and diphenyl derivatives with electron-accepting groups in a *para* position. In this series, therefore, it appears that electron-donating substituents favour, and electron-accepting substituents inhibit, compound formation. Of interest from this point of view is the formation of a highly coloured and stable compound from 4-nitrodiphenyl and *NNN′N′*-tetramethylbenzidine (which contains strongly electron-donating dimethylamino-groups). This compound is the only stable and easily prepared molecular complex formed by a simple mononitro-derivative which is known to us, and is the only compound formed by 4-nitrodiphenyl which we have isolated. (A red colour is produced when solutions of 4-nitrodiphenyl and benzidine are mixed; but we have not succeeded in isolating the complex formed.)

In a series of *X*-ray crystallographic studies (shortly to be published elsewhere) the crystal structures of six of the molecular compounds listed in Table I have been examined, namely, those from 4-hydroxy- and 4 : 4′-

dihydroxy-diphenyl, benzidine, *NNN'N'*-tetramethylbenzidine, and 4-iodo- and 4-bromo-diphenyl. The structure of the first of these complexes has been worked out in detail, and the studies of the others carried sufficiently far to demonstrate that they all possess structures of the type indicated in the figure. In this projected structure the dinitrodiphenyl (acceptor) molecules are to be seen one above the other separated by 3·7 A., whilst the donor molecules are seen end-on perpendicular to the plane of the paper. In the actual structures geometrical and symmetry considerations require that individual molecules should be tilted in varying degrees; but the type of structure still remains essentially the same as the idealized structure of the figure.

The following are significant points arising from the crystallographic studies:

(*a*) In the molecular compound with 4-hydroxydiphenyl (a complete *X*-ray crystallographic analysis of which has been carried out) all the molecules are approximately equally spaced from one another, and none of the intermolecular distances is shorter than those normally found *in crystals of aromatic nitro-compounds*, bonding in which is attributed to ordinary van der Waals forces (Table II). The only exception is *one* OH—O distance of 3·0 A. At this distance very weak hydrogen bonding *might* be possible; but this could not explain compound formation, because the molecular ratio of the components is 3 : 1. The closest intermolecular approaches are those between the oxygen atoms of the nitro-groups and the carbon atoms of the benzene rings; but it is unlikely that these could provide a mechanism for compound formation, particularly as the approach of the nitro-groups to the benzene rings of the hydroxydiphenyl molecules is no closer than their approach to the benzene rings of the dinitrodiphenyl molecules themselves. The *X*-ray data, like those of Powell, Huse, and Cooke (*J.*, 1943, 153) on the complex between *s*-trinitrobenzene and *p*-iodoaniline, therefore reveal no localized bonding between the units in the crystal structure. The same almost certainly holds good for the other compounds in Table I for which preliminary structures have been worked out: in no cases is there any necessity to assume closer approaches between the molecules of the components than those determined for the dinitrodiphenyl–hydroxydiphenyl complex; *i.e.*, there is sufficient space in the unit cell in each case for the molecules to pack quite normally. Furthermore, the crystal densities (Table I) are quite normal, and no higher than those recorded for the aromatic nitro-compounds listed in Table II.

TABLE II.

*Distances* (A.) *of Closest Intermolecular Approach observed in Various Compounds.*

| Compound. | O–O Distance between oxygen atoms of nitro-groups. | O–C Distance from oxygen atom of nitro-group to carbon of benzene ring. | C–C Distance [6] between carbon atoms of adjacent molecules. |
|---|---|---|---|
| Molecular compound of 4 : 4′-dinitrodiphenyl with 4-hydroxydiphenyl [1] ... | 3·5 | 3·2 | 3·6 |
| *p*-Dinitrobenzene [2] ..... | 3·1(9) | 3·3(0) | 3·6(3) |
| *m*-Dinitrobenzene [3] ..... | 3·2(0) | 2·9(5) | 3·6(0) |
| 4 : 4′-Dinitrodiphenyl [4] ..... | 3·4 | 2·9 | 3·6 |
| Molecular compound of *s*-trinitrobenzene with *p*-iodoaniline [5] ..... | 3·2(5) | 3·3(5) | 3·5 |

[1] Saunder, shortly to be published elsewhere. [2] James, King, and Horrocks, *Proc. Roy. Soc.*, 1935, *A*, **153**, 225. [3] Archer, unpublished work. [4] van Niekerk, *Proc. Roy. Soc.*, 1943, *A*, **181**, 314. [5] Powell, Huse, and Cooke, *J.*, 1943, 153. [6] Compare also the C–C distances of 3·60—3·72 A. for naphthalene, and 3·77—3·80 A. for anthracene (Robertson, *Proc. Roy. Soc.*, 1933, *A*, **140**, 79).

(*b*) In all these complexes very pronounced thermal vibrations occur, as shown by the strong "optical ghosts" accompanying certain spectra. This is an indication of comparatively weak bonding between the "layers" of atoms concerned, and is most pronounced for the spectra arising from the planes most nearly containing the dinitrodiphenyl molecules. There is thus weak bonding between these units in the crystal structure. Powell and Huse (*J.*, 1943, 435) have found similar diffuse spectra in the complex of hexamethylbenzene with picryl chloride, indicating weak bonding between layers consisting each of one kind of molecule.

(*c*) In the cases of the complexes of 4-iodo- and 4-bromo-diphenyl with 4 : 4′-dinitrodiphenyl, further optical ghosts (distinct from those produced by thermal vibration) have been observed. These optical ghosts are the result of a periodic error in the structure, the nature of which is still under investigation. It is perhaps significant that these two complexes are amongst the most lightly coloured and least stable of the series of compounds examined. Powell and Huse (*loc. cit.*) have also observed similar optical ghosts in the study of the complex of hexamethylbenzene with picryl chloride, and have suggested that in this case errors in the structure are due to alternate layers of molecules not being completely regular; *i.e.*, sometimes two adjacent layers of the same type of molecule may exist.

(*d*) It seems clear that the molecular ratios in which the components unite are determined almost exclusively by geometrical considerations. In compounds conforming to the type of structure depicted in the figure the number of 4 : 4′-dinitrodiphenyl molecules that can be accommodated by each molecule of the "donor" component depends on the length of the molecule of this component. In Table I are listed molecular ratios calculated on this basis for a number of compounds, together with the ratios actually observed. The agreement between the observed and the calculated values is surprisingly good in view of the differences which are to be expected in consequence of the tilting of the various molecules. It seems evident that the exact stoicheiometric

ratios observed in these molecular compounds are a result more of the requirements of crystal structure than of any specific bonding mechanism.

## Experimental.

*Preparation of Molecular Compounds.*—All the molecular compounds of 4 : 4′-dinitrodiphenyl, except the 1 : 1 compound with *NNN′N′*-tetramethylbenzidine, were prepared as follows. A considerable excess of the "donor" component dissolved in acetone (in the case of tetramethylbenzidine, in chloroform) was added to a boiling, almost saturated solution of 4 : 4′-dinitrodiphenyl in acetone. The crystals of the molecular compound which separated on slow cooling were filtered off rapidly, washed on the filter with a little acetone, and dried.

1 : 1-*Compound of* 4 : 4′-*dinitrodiphenyl and* NNN′N′-*tetramethylbenzidine.* A solution of 4 : 4′-dinitrodiphenyl in acetone was added to a considerable excess of *NNN′N′*-tetramethylbenzidine dissolved in chloroform, both solutions being at room temperature. Crystals of the molecular compound separated immediately. An attempt to prepare a 1 : 1 compound with benzidine was unsuccessful.

1 : 1 *Compound of* 4-*nitrodiphenyl and* NNN′N′-*tetramethylbenzidine.* This could be prepared from the components in acetone solution by the general method described above; but it was most conveniently made by adding the tetramethylbenzidine in chloroform solution to a hot, well-stirred solution of 4-nitrodiphenyl in alcohol. A deep red coloration appeared on mixing, and the compound separated in rouge-coloured crystals, m. p. 150°.

*Compound formation between* 4-*nitrodiphenyl and benzidine.* When solutions of 4-nitrodiphenyl and benzidine in acetone or alcohol were mixed a bright red coloration appeared. No compound could be isolated, however, although the relative concentrations of the components were varied over a wide range.

No crystals other than those of the components were isolated, and no colour was generated in solution, when 4 : 4′-dinitrodiphenyl was treated with :

(*a*) the following compounds containing electron-donating groups in *ortho* position : 2 : 2′-diamino-, 2-amino-, 2-hydroxy-, 2 : 2′-di-iodo-, and 2 : 2′-dibromo-diphenyl;

(*b*) the following compounds containing electron-accepting groups in *para* position : diphenyl-4-carboxylic and -4 : 4′-dicarboxylic acid, and 4-acetyldiphenyl.

*Analysis of Molecular Compounds.*—The *compounds* with amines were decomposed by digestion with 5N-hydrochloric acid (90% formic acid in the case of 4-aminodiphenyl, on account of the insolubility of the hydrochloride), and the nitro-compound was separated by filtration from the solution of the amine hydrochloride, washed with water, dried at 80—90°, and weighed. The amine was precipitated from the filtrate with alkali, filtered off, washed with water, dried, and weighed.

An analogous procedure was used for *compounds* with phenols, decomposition being effected with 5N-sodium hydroxide solution instead of hydrochloric acid.

| | | | | |
|---|---|---|---|---|
| 4 : 4′-Dinitrodiphenyl | + tetramethylbenzidine | (4 : 1). | Found : ratio, | 3·96, 4·01. |
| | + tetramethylbenzidine | (1 : 1) | ,, ,, | 0·98, 1·01. |
| | + benzidine | (4 : 1) | ,, ,, | 3·89, 3·99. |
| | + 4-aminodiphenyl | (3 : 1) | ,, ,, | 2·96, 3·01. |
| | + 4 : 4′-dihydroxydiphenyl | (3 : 1) | ,, ,, | 2·96, 3·06. |
| | + 4-hydroxydiphenyl | (3 : 1) | ,, ,, | 3·10, 3·12. |
| 4-Nitrodiphenyl | + tetramethylbenzidine | (1 : 1) | ,, ,, | 1·02, 1·03. |

The compositions of the remaining *complexes* were found by determining their nitrogen contents.

4 : 4′-Dinitrodiphenyl + 4 : 4′-diacetoxydiphenyl (5 : 1). Found : N, 9·35, 9·38. $5C_{12}H_8O_4N_2,C_{16}H_{14}O_4$ requires N, 9·40%.

+ 4-acetoxydiphenyl (4 : 1). Found : N, 9·40, 9·47. $4C_{12}H_8O_4N_2,C_{14}H_{12}O_2$ requires N, 9·43%.

+ 4 : 4′-dimethoxydiphenyl (3·5 : 1). Found : N, 9·14, 9·21. $3{\cdot}5C_{12}H_8O_4N_2,C_{14}H_{14}O_2$ requires N, 9·18%.

+ 4-iododiphenyl (3·5 : 1). Found : N, 8·58, 8·65. $3{\cdot}5C_{12}H_8O_4N_2,C_{12}H_9I$ requires N, 8·64%.

+ 4-bromodiphenyl (3·5 : 1). Found : N, 8·97, 9·03. $3{\cdot}5C_{12}H_8O_4N_2,C_{12}H_9Br$ requires N, 9·01%.

+ diphenyl (3 : 1). Found : N, 9·53, 9·53. $3C_{12}H_8O_4N_2,C_{12}H_{10}$ requires N, 9·48%.

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# 247. *Steric Inhibition of Resonance. Part III. The Basic Strengths of Some Dimethyl-substituted Aromatic Primary and Tertiary Amines.*

By George Thomson.

The p$K_a$ values of a series of methyl-substituted anilines and dimethylanilines have been measured at 25° in aqueous-alcoholic solution. Dimethyl-*m*-2-xylidine is found to differ little in strength from dimethyl-*m*-5-xylidine in such solutions. Doubt is expressed as to whether resonance plays so large a part as has been attributed to it in determining the strength of aromatic tertiary bases.

The value of the molecular refractivity of dimethyl-*p*-xylidine is found to be in accordance with views expressed in Part II of this series (*J.*, 1944, 408).

It has been suggested (Baddeley, *Nature*, 1939, **144**, 444; Branch and Calvin, "The Theory of Organic Chemistry," New York, 1941, 260; Wheland, "The Theory of Resonance," New York 1944, 189) that the higher basicity of dimethyl-*o*-toluidine than of its *m*- and *p*-isomerides (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469; Davies and Addis, *J.*, 1937, 1622) is due to steric inhibition by the *o*-methyl substituent of the resonance of the dimethylamino-group with the benzene nucleus. If this explanation is well founded, intro-

duction of a second methyl group ortho to the dimethylamino-group would be expected to result in a considerable increase in basic strength: Hampson and Ingham (*J.*, 1939, 981) have shown from dipole-moment measurements that in dimethylmesidine and nitrodimethylaminodurene resonance of the dimethylamino-group with the benzene nucleus is almost completely suppressed, and in Part II of this series (*loc. cit.*) it was shown that the atomic refractivity of the nitrogen atom in *N*-dimethyl-*m*-2-xylidine approximates to that observed in aliphatic tertiary amines. But Davies and Addis (*loc. cit.*) found that in 50% aqueous alcohol at 20° dimethylmesidine ($pK_a$* 5·15) was only a slightly stronger base than dimethyl-*o*-toluidine ($pK_a$ 5·07). It was therefore decided to measure the basic strengths of some *N*-dimethylxylidines and of the parent xylidines; for comparison, measurements were made under similar conditions on aniline, dimethylaniline, *o*-toluidine, and dimethyl-*o*-toluidine. The method adopted was measurement of the pH values of a series of mixtures of base and standard hydrochloric acid solution, a glass electrode being used with a saturated potassium chloride–calomel half-cell as reference electrode. Because of the low solubility in water of the tertiary amines, solutions in 50% and in 75% aqueous ethyl alcohol were used and, in view of uncertainty as to the value of $K_w$ in those alcoholic solutions, the results are expressed as $pK_a$ for the conjugate acids (calculated by means of the simple Henderson equation $pK_a = pH + \log [salt]/[base]$).

*Discussion of Results.*—The results are summarised in Table I. All measurements are at 25°.

TABLE I.

| | In 50% alcohol. Mean p*K*. | In 75% alcohol. Mean p*K*. | | In 50% alcohol. Mean p*K*. | In 75% alcohol. Mean p*K*. |
|---|---|---|---|---|---|
| Aniline ..... | 4·25 | 3·98 | Dimethylaniline ..... | 4·26 | 3·84 |
| *o*-Toluidine ..... | 3·98 | — | Dimethyl-*o*-toluidine ... | 5·07 | 4·47 |
| *m*-2-Xylidine ..... | 3·42 | 3·19 | Dimethyl-*m*-2-xylidine ... | 4·69 | 4·26 |
| *m*-4-Xylidine ..... | 4·61 | 4·35 | Dimethyl-*m*-4-xylidine ... | 5·28 | 4·76 |
| *m*-5-Xylidine ..... | 4·48 | 4·30 | Dimethyl-*m*-5-xylidine ... | 4·48 | 4·11 |
| *p*-Xylidine ..... | 4·17 | 4·00 | Dimethyl-*p*-xylidine ... | 5·19 | 4·62 |

The $pK_a$ value (4·26) found for dimethylaniline in 50% alcohol is a little higher than would be expected from Davies and Addis's value (*loc. cit.*) (4·21 at 20°), since Hall and Sprinkle (*loc. cit.*) found the temperature coefficient of $pK_a$ to be negative; the same is true of the value found for dimethyl-*o*-toluidine, which is identical with that found by Davies and Addis (*loc. cit.*). These differences, however, are not serious and may possibly be due to slight differences in the solvents. Change of solvent from 50% to 75% alcohol affects the $pK_a$ values for the primary amines much less than those for the tertiary amines; if the $pK_a$ values are plotted against vol.-% of alcohol and the points for each substance are joined by straight lines, it is found that the slopes of the lines for the tertiary amines are all similar but steeper than those for the primary amines, which in turn are similar (cf. Wynne-Jones, *Proc. Roy. Soc.*, 1933, *A*, **140**, 440). The relative $pK_a$ values for the primary bases in the two solvents are closely parallel: the ratio $pK_a$ xylidine/$pK_a$ aniline which varies from xylidine to xylidine has for any given xylidine much the same value (within 2—3%) in 50% alcohol and in 75% alcohol, and the same holds true for the tertiary bases (taking for them the ratio $pK_a$ tertiary amine/$pK_a$ dimethylaniline). It will be noticed that dimethylaniline, which in aqueous solution is a stronger base than aniline (Hall, *J. Amer. Chem. Soc.*, 1930, **52**, 5115; Hall and Sprinkle, *loc. cit.*), appears in 50% alcohol to be identical in strength with aniline but in 75% alcohol to be weaker; also that dimethyl-*m*-5-xylidine in 50% alcohol appears identical in strength with *m*-5-xylidine whereas the latter is the stronger in 75% alcohol. It would, therefore, appear valid to compare among themselves basic strengths of nuclear-substituted anilines or nuclear-substituted dimethylanilines in any one solvent [cf. Bennett, Brooks, and Glasstone (*J.*, 1935, 1821), who concluded that " the strength of a series of acids or bases *of the same type* should be in the same order in all solvents provided there be no complicating side reactions of a purely chemical nature "]; on the other hand, arguments based on comparisons between basic strengths of primary and tertiary amines seem of questionable validity in view of the uncertainty that the dissociation constant of the base in any solvent—even in water—is a true measure of the intrinsic strength of the base, that is, of its tendency to gain a proton.

From the data in Table I it is evident that introduction into dimethylaniline of one methyl group in the *o*-position results in an increase of $pK_a$ but that introduction of a second methyl group in the other *o*-position as in dimethyl-*m*-2-xylidine results, not in a further increase, but in a decided decrease in $pK_a$; introduction of the second nuclear methyl group para to the dimethylamino-group as in dimethyl-*m*-4-xylidine, or meta to the dimethylamino-group and para to the first nuclear methyl group as in dimethyl-*p*-xylidine, results in an increase of $pK_a$, slightly greater in the first case than in the second but in each case of the same order of magnitude as the decrease resulting from the introduction of the second methyl group in the *o*-position.

Further, the astonishing fact emerges that dimethyl-*m*-5-xylidine, in which both nuclear methyl groups are meta to the dimethylamino-group and no question of steric inhibition of resonance can arise, does not have a $pK_a$ value widely different from that of dimethyl-*m*-2-xylidine. The evidence of other properties suggests that there can be little doubt that substitution of two methyl groups ortho to a dimethylamino-group does almost completely suppress resonance between that group and the benzene nucleus, but the closeness of the values of $pK_a$ for dimethyl-*m*-2- and -*m*-5-xylidine raises doubt whether resonance plays so large a part as has been

* Throughout this paper bases are compared by reference to the $pK_a$ values for their conjugate acids.

attributed to it in determining the strength of aromatic tertiary bases: if it did, one would expect a difference of at least 3 or 4 logarithmic units (*i.e.*, a difference approaching in magnitude the difference in p$K_a$ between an aromatic and an aliphatic tertiary base) instead of the observed difference of less than 0·3 logarithmic unit. Doubt is strengthened by the data of Table II.

TABLE II.

| | p$K_a$. | | p$K_a$. |
|---|---|---|---|
| *o*-Toluidine | 4·39 * | *o*-Anisidine | 4·49 * |
| *p*-Toluidine | 5·12 * | *p*-Anisidine | 5·29 * |
| Dimethyl-*o*-toluidine | 5·86 * | Dimethyl-*o*-toluidine | 5·07 † |
| Dimethyl-*p*-toluidine | 5·50 * | Dimethyl-*p*-toluidine | 4·77 † |
| Diethyl-*o*-toluidine | 7·18 * | Dimethyl-*o*-anisidine | 5·49 † |
| Diethyl-*p*-toluidine | 7·09 * | Dimethyl-*p*-anisidine | 5·16 † |

* In water at 25° (Hall and Sprinkle, *loc. cit.*).
† In 50% alcohol at 20° (Davies and Addis, *loc. cit.*).

*o*-Anisidine has a p$K_a$ value comparable with that for *o*-toluidine, yet the p$K_a$ value for dimethyl-*o*-anisidine exceeds that for dimethyl-*o*-toluidine by rather more than the amount by which the p$K_a$ value for the latter exceeds that for dimethyl-*p*-toluidine; the latter difference has been attributed to inhibition of resonance in dimethyl-*o*-toluidine. The enhanced basicity of dimethyl-*o*-anisidine can hardly be attributed to the steric effect of the methoxyl group, an effect which has been shown to be considerably less than that of methyl [cf., *e.g.*, the work of Adams and his co-workers (*J. Amer. Chem. Soc.*, 1940, **62**, 2191; 1941, **63**, 2859) on restricted rotation in arylamines]. It appears significant also that the difference in p$K_a$ between diethyl-*o*- and -*p*-toluidine should be so much smaller than that between the corresponding dimethyl compounds; greater steric incompatibility would be expected between the diethylamino-group and an *o*-methyl group than between the dimethylamino-group and an *o*-methyl group.

The nuclear methyl-substituted anilines present a marked contrast to the dimethylanilines: introduction of *o*-methyl groups leads to a progressive reduction of p$K_a$, and we have aniline > *o*-toluidine > *m*-2-xylidine, whereas in the *N*-dimethyl derivatives the order is dimethyl-*o*-toluidine > dimethyl-*m*-2-xylidine > dimethylaniline.

Further work on disubstituted aromatic bases is in progress.

*Note on the Molecular Refractivity of Dimethyl*-p-*xylidine.*—The molecular refractivity of dimethyl-*p*-xylidine for sodium yellow is found to be 49·61 c.c. Landolt and Jahn (*Z. physikal. Chem.*, 1892, **10**, 289) found for *p*-xylene $[R_L]_D$ 35·95 c.c. The difference, 13·66 c.c., is in close agreement with the difference, 13·62 c.c., between dimethyl-*m*-4-xylidine and *m*-xylene recorded in Part II of this series (*loc. cit.*) and corroborates the conclusion there reached that, whenever methyl or chlorine is substituted ortho to the dimethylamino-group, the group refraction of the latter group suffers a reduction of approximately 1 c.c.

## EXPERIMENTAL.

The specimens of dimethylaniline, *m*-2- and *m*-4-xylidines and their *N*-dimethyl derivatives, and *N*-dimethyl-*m*-5-xylidine were those used in the work described in Part II (*loc. cit.*). They were redistilled before use. *m*-5-Xylidine was a fresh specimen prepared by Haller and Adams's method (*J. Amer. Chem. Soc.*, 1920, **42**, 1840). Aniline was prepared by hydrolysis of a pure specimen of acetanilide. *p*-Xylidine, prepared from the hydrochloride (Eastman Kodak Company), had b. p. 215·4°/749 mm., $d_4^{25°}$ 0·97140, $n_D^{25°}$ 1·55752, $n_{5461}^{25°}$ 1·56282; $[R_L]_D$ is therefore 40·13 (Brühl, *Z. physikal. Chem.*, 1895, **16**, 193, gives 39·95). *N*-Dimethyl-*p*-xylidine, prepared by methylation with methyl sulphate (Evans and Williams, *J.*, 1939, 1199), had b. p. 202—202·2°/756 mm., $d_4^{25°}$ 0·91406, $n_D^{25°}$ 1·52073, $n_{5461}^{25°}$ 1·52503, whence $[R_L]_D$ 49·61, $[R_L]_{5461}$ 49·95 (Brown, Widiger, and Letang, *J. Amer. Chem. Soc.*, 1939, **61**, 2597, give b. p. 199°/745 mm., $n_D^{20°}$ 1·5223). Dimethyl-*o*-toluidine (B.D.H.) was treated with *p*-toluenesulphonyl chloride to remove any primary or secondary base; it had b. p. 183·4°/757 mm. *o*-Toluidine (from aceto-*o*-toluidide) had b. p. 199°/759 mm.

pH values were measured by using a Marconi–Ekco pH meter.

Solutions were prepared as follows: in "50% alcohol" by dissolving *w* g. of base in rather less than 50 ml. of ethyl alcohol, adding 50 ml. of 0·01N-aqueous hydrochloric acid, and making the volume up to 100 ml. with ethyl alcohol in a standard flask; in "75% alcohol" by a similar procedure but using only 25 ml. of 0·01N-acid.

| 50% Alcohol. | | | 75% Alcohol. | | |
|---|---|---|---|---|---|
| *w.* | pH. | p*K*. | *w.* | pH. | p*K*. |
| | | Dimethylaniline. | | | |
| 0·3378 | 4·79 | 4·24 | 0·1709 | 4·43 | 3·87 |
| 0·2581 | 4·56 | 4·27 | 0·2580 | 4·64 | 3·87 |
| | Mean | 4·26 | 0·1771 | 4·45 | 3·88 |
| | | | | Mean | 3·87 |
| | | Dimethyl-*m*-2-xylidine. | | | |
| 0·1188 | 4·43 | 4·66 | 0·1993 | 4·86 | 4·22 |
| 0·0827 | 3·78 | 4·74 | 0·1125 | 4·56 | 4·26 |
| 0·1133 | 4·40 | 4·68 | 0·0807 | 4·35 | 4·28 |
| 0·1102 | 4·36 | 4·68 | 0·1608 | 4·81 | 4·29 |
| | Mean | 4·69 | 0·1098 | 4·55 | 4·25 |
| | | | | Mean | 4·26 |

| 50% Alcohol. | | | 75% Alcohol. | | |
|---|---|---|---|---|---|
| *w.* | pH. | p*K*. | *w.* | pH. | p*K*. |
| | | Dimethyl-*m*-4-xylidine. | | | |
| 0·0989 | 4·78 | 5·27 | 0·1700 | 5·35 | 4·80 |
| 0·1143 | 5·02 | 5·29 | 0·1184 | 5·08 | 4·74 |
| 0·0979 | 4·76 | 5·26 | 0·0976 | 4·95 | 4·74 |
| 0·1481 | 5·30 | 5·30 | 0·1811 | 5·31 | 4·72 |
| | Mean | 5·28 | 0·1365 | 5·22 | 4·80 |
| | | | 0·0987 | 5·00 | 4·78 |
| | | | | Mean | 4·76 |
| | | Dimethyl-*m*-5-xylidine. | | | |
| 0·1273 | 4·32 | 4·47 | 0·1500 | 4·59 | 4·11 |
| 0·1093 | 4·14 | 4·47 | 0·1654 | 4·62 | 4·08 |
| 0·1456 | 4·43 | 4·45 | 0·1078 | 4·40 | 4·12 |
| | Mean | 4·46 | 0·0732 | 4·11 | 4·12 |
| | | | 0·2196 | 4·83 | 4·14 |
| | | | | Mean | 4·11 |

| 50% Alcohol. | | | 75% Alcohol. | | |
|---|---|---|---|---|---|
| *w.* | pH. | p*K*. | *w.* | pH. | p*K*. |
| | Dimethyl-*p*-xylidine. | | | | |
| 0·1938 | 5·40 | 5·18 | 0·3100 | 5·47 | 4·61 |
| 0·1184 | 4·97 | 5·19 | 0·2507 | 5·37 | 4·61 |
| 0·1714 | 5·30 | 5·19 | 0·1701 | 5·18 | 4·63 |
| 0·0998 | 4·73 | 5·20 | 0·1393 | 5·07 | 4·63 |
| | Mean | 5·19 | | Mean | 4·62 |
| | Dimethyl-*o*-toluidine. | | | | |
| 0·2980 | 5·58 | 5·05 | 0·2610 | 5·30 | 4·47 |
| 0·4615 | 5·85 | 5·08 | 0·3929 | 5·52 | 4·49 |
| 0·2097 | 5·39 | 5·07 | 0·4994 | 5·60 | 4·46 |
| 0·4199 | 5·79 | 5·07 | 0·5850 | 5·67 | 4·46 |
| | Mean | 5·07 | | Mean | 4·47 |
| | Aniline. | | | | |
| 0·3758 | 5·11 | 4·26 | 0·2968 | 5·03 | 3·98 |
| 0·2987 | 4·95 | 4·24 | 0·4134 | 5·20 | 3·98 |
| 0·5212 | 5·28 | 4·27 | 0·2357 | 4·95 | 3·99 |
| | Mean | 4·26 | | Mean | 3·98 |
| | *m*-2-Xylidine. | | | | |
| 0·2185 | 3·82 | 3·40 | 0·1717 | 3·84 | 3·17 |
| 0·2612 | 3·95 | 3·43 | 0·2351 | 4·06 | 3·23 |
| 0·3045 | 4·00 | 3·40 | 0·3293 | 4·20 | 3·21 |
| 0·3801 | 4·15 | 3·43 | 0·2123 | 3·92 | 3·14 |
| | Mean | 3·42 | | Mean | 3·19 |

| 50% Alcohol. | | | 75% Alcohol. | | |
|---|---|---|---|---|---|
| *w.* | pH. | p*K*. | *w.* | pH. | p*K*. |
| | *m*-4-Xylidine. | | | | |
| 0·2486 | 5·09 | 4·60 | 0·2612 | 5·25 | 4·37 |
| 0·3393 | 5·27 | 4·61 | 0·2154 | 5·12 | 4·33 |
| | Mean | 4·61 | 0·3267 | 5·25 | 4·36 |
| | | | | Mean | 4·35 |
| | *m*-5-Xylidine. | | | | |
| 0·2988 | 5·07 | 4·47 | 0·2335 | 5·12 | 4·29 |
| 0·4401 | 5·28 | 4·48 | 0·3825 | 5·39 | 4·32 |
| 0·2116 | 4·90 | 4·50 | 0·5297 | 5·52 | 4·30 |
| | Mean | 4·48 | | Mean | 4·30 |
| | *p*-Xylidine. | | | | |
| 0·2569 | 4·70 | 4·19 | 0·3811 | 5·07 | 4·01 |
| 0·2943 | 4·76 | 4·17 | 0·3208 | 4·97 | 3·99 |
| 0·3637 | 4·85 | 4·15 | | Mean | 4·00 |
| 0·5342 | 5·06 | 4·17 | | | |
| | Mean | 4·17 | | | |
| | *o*-Toluidine. | | | | |
| 0·4531 | 4·85 | 3·98 | | | |
| 0·5249 | 4·92 | 3·97 | | | |
| 0·2241 | 4·48 | 3·98 | | | |
| | Mean | 3·98 | | | |

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## 248. *The Application of the Method of Molecular Rotation Differences to Steroids. Part III. Steroidal Hormones and Bile Acids.*

By D. H. R. BARTON.

The data available in the literature on the optical rotatory powers of steroidal hormones and bile acids have been correlated, and comparison is made with similar work in the sterol field (see Barton, Part I, *J.*, 1945, 813; Part II, this vol., p. 512). A comparatively small number of the steroids considered in this paper possess anomalous rotatory powers which, it is suggested, are due to the preparations concerned being impure.

Physical considerations lead to the formulation of *ψ*-ergostane and its derivatives and of coprostadienols B and D. The application of optical rotatory power evidence in the unsaturated bile acid field results in a clarification of conflicting data and the formulation of various substances including the α- and β-dihydroxycholadienic acids and β-apocholic acid.

Finally there is a short note on the relationship between melting point and structure in the steroid field and, as an example, the characterisation of the nuclear double bond of the mixed stellasterols as $\Delta^7$ is mentioned.

PREVIOUS communications (Barton, *locc. cit.*) have shown how useful a critical study of optical rotatory power can be in the steroid field. All the substances so far considered have, however, been members of the *allo*-cholane type with rings A and B fused in the *trans*-position and with the 3 hydroxyl in the (β) configuration [see formula (I) below]. Many other naturally occurring substances of the steroid group have different arrangements in these two rings. For example androsterone is of type (II), the oestrogenic hormones have ring A, aromatic, the bile acids are of type (IV), whilst, for contrast, progesterone, corticosterone, and testosterone are $\Delta^4$-3-ketones. Representatives of all the four types [formulæ (I) to (IV) below] are found in the cardiac aglycone and steroidal sapogenin fields. $\Delta^5$-Steroids of type (V) occur in Nature and are possible precursors of many of the other steroids, but compounds of type (VI) are rarely met even in synthetic work.

Just as the optical rotation changes on acylation of the $C_3$ hydroxyl are characteristic in differentiating naturally occurring sterols from triterpenes (Part I), so are the corresponding rotational changes for substances of types (II) to (IV) uniquely characteristic of the molecular environment of the hydroxyl in ring A. Owing, however, to the limited recording of rotational data only $\Delta_1$ values (for definition see Part I) can be considered in detail; these are summarised in Table I. All the relevant observations in the literature have been collected for bile acids and steroidal hormones and treated as described previously (Part I), although, in order to conserve space, compounds are not mentioned individually. The term "bile acid" is used generically to include esters and other closely related derivatives that have been prepared in recent years, whilst the term "steroidal hormone" includes the natural androgenic hormones and all natural and synthetic analogues in both the androstane and the pregnane series. Rotational values in chloroform have not usually been available and comparison has been made, therefore, between the values recorded for the acetate and its parent alcohol both in some other solvent.

TABLE I.

| Substance class. | Formula type. | Solvent. | A.M.* of $\Delta_1$ values. | No. of examples. | Limits of variation from A.M. | References. |
|---|---|---|---|---|---|---|
| Stanols | (I) | $CHCl_3$ | −34 | 7 | + 8 to −11 | 1. |
| Bile acids and steroidal hormones † | (I) | All | −17 | 12 | +16 to −20 | 2, 3, 4, 5, 6, 7, 8, 9, 10, 11. |
| Stanols | (II) | $CHCl_3$ | +29 | 2 | + 8 to − 9 | 12, 13, 14. |
| Bile acids and steroidal hormones † | (II) | All | +24 | 7 | +13 to −23 | 4, 12, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25. |
| Bile acids † | (III) | $Me_2CO$ | +17 | 5 | +13 to −17 | 26, 27, 28, 29, 30. |
| Stanols | (IV) | All | +77 | 3 | +14 to −18 | 31, 32. |
| Bile acids and steroidal hormones † | (IV) | All | +83 | 21 | +23 to −29 | 26, 27, 29, 33, 34, 35, 36, 37, 38, 39, 40, 41. |
| $\Delta^5$-Stenols | (V) | $CHCl_3$ | −35 | 12 | +15 to −10 | 1. |
| Bile acids and steroidal hormones † | (V) | All | −28 | 32 | +25 to −23 | 2, 3, 6, 8, 33, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63 64, 65, 66, 70. |

* Arithmetic mean. All rotations are for the $Na_D$ line.
† For definitions of compounds included under these headings see text.

There is good reason, however, to believe, that $\Delta_1$ values in chloroform are not very different from those in other solvents (cf. Plattner and Heusser, *Helv. Chim. Acta*, 1944, **27**, 748) and a number of determinations have

TABLE II.

| Substance. | $\Delta_1$ values. Acetone. | Alcohol. | Chloroform. | Dioxan. |
|---|---|---|---|---|
| Cholesterol | −35 | −21 | −34 (−35 *) | −32 |
| Dehydro*iso*androsterone | — | −17 | −29 | — |
| Cholestanol | −31 | −31 | −29 (−34 *) | −28 |
| *iso*Androsterone | — | −27 | −32 | — |

* Mean values from analysis of literature (see Part I).

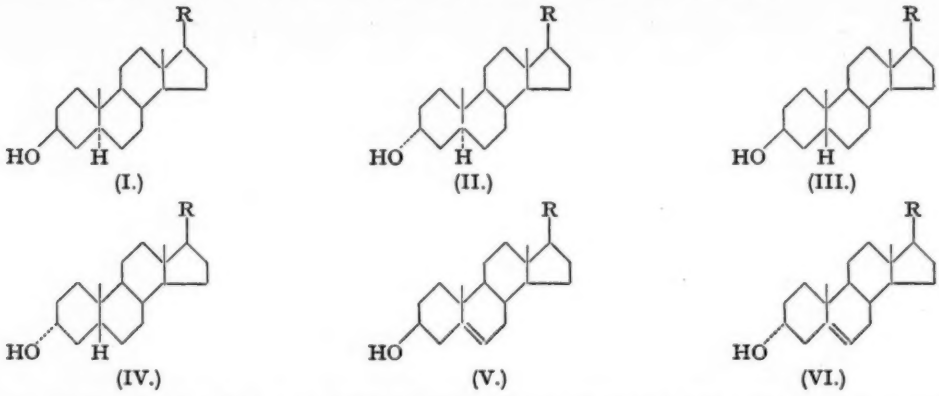
been made (Table II) which confirm this view. Most of the examples quoted in Table I are substituted in the side chain and/or in ring C, but no striking and unambiguous examples of vicinal action can be reported.

TABLE III.

| Substance. | Formula type. | Solvent. | $[M]_D$. Alcohol. | Acetate. | $\Delta_1$. | Refs. |
|---|---|---|---|---|---|---|
| *Bile acids :* | | | | | | |
| 3(β) : 11(β) : 17(β)-Trihydroxy*allo*ætiocholanic acid methyl ester | (I) | $C_4H_8O_2$ | + 29 | + 45 | + 16 | 4 |
| 3(α)-Hydroxybisnor*allo*cholanic acid methyl ester | (II) | $CHCl_3$ | + 43 | + 40 | − 3 | 12 |
| 3(β)-Hydroxy-11-ketocholanic acid methyl ester | (III) | $Me_2CO$ | +158 | +250 | + 92 | 67 |
| 3(α)-Hydroxy-12-ketonorcholanic acid | (IV) | $C_4H_8O_2$ | +263 | +418 | +155 | 68 |
| 3(α)-Hydroxy-12-ketobisnorcholanic acid | (IV) | $C_4H_8O_2$ | +308 | +267 | − 41 | 68 |
| 3(β) : 17-Dihydroxy-$\Delta^5$-androsten-17-acetic acid methyl ester | (V) | $CHCl_3$ | −322 | −275 | + 47 | 47 |
| 3(β)-Hydroxy-$\Delta^{5,16}$-ætiocholadienic acid methyl ester | (V) | $CHCl_3$ | −165 | −257 | − 92 | 42 |
| *Steroidal hormones :* | | | | | | |
| 3(β)-Hydroxy-20-*iso*ternor*allo*cholanyl methyl ketone | (I) | $CHCl_3$ | + 41 | + 46 | + 5 | 6 |
| *allo*Pregnan-3(α)-ol-20-one | (II) | $C_2H_5OH$ | +280 | +342 | + 62 | 10 |
| Pregnan-3(β)-ol-20-one | (III) | $C_2H_5OH$ | +321 | +310 | − 11 | 39 |
| $\Delta^5$-Pregnen-3(β)-ol-20-one-21-al diethyl mercaptal | (V) | $Me_2CO$ | +602 | +717 | +115 | 49 |
| 21-Bromacetoxy-$\Delta^5$-pregnen-3(β)ol-20-one | (V) | $CHCl_3$ | +113 | +129 | + 16 | 69 |
| 3(β)-Hydroxy-$\Delta^5$-20-*iso*ternorcholenyl phenyl ketone | (V) | $CHCl_3$ | −191 | −193 | − 2 | 48 |
| 3(β)-Hydroxy-$\Delta^5$-ternorcholenyl mesityl ketone | (V) | $CHCl_3$ | −278 | −264 | + 14 | 48 |
| 3(β)-Hydroxy-$\Delta^5$-ternorcholenyl methyl ketone | (V) | $CHCl_3$ | −240 | −307 | − 67 | 48 |
| 3(β)-Hydroxy-$\Delta^5$-ternorcholenyl *iso*amyl ketone | (V) | $CHCl_3$ | −219 | −277 | − 58 | 48 |

A number of bile acid and steroidal hormone derivatives have $\Delta_1$ values which are completely incompatible with their allotted structures. These are listed in Table III, and it is confidently predicted that repetition of the preparation of these substances will lead to extensive revision of their recorded rotations.

The predicted revised $\Delta_1$ values can, of course, be read off from Table I. It is significant that 5 of the 16 cases of anomalous $\Delta_1$ values are drawn from one investigation (references 6 and 48).




(I.) (II.) (III.) (IV.) (V.) (VI.)

Although, as mentioned above, $\Delta_1$ values are roughly the same in all the solvents examined, it is not necessarily true that $\Delta$ values in general are the same in all solvents. Thus there is a small, but definite, decrease in the $\Delta$ values for the reduction of $\Delta^5$ double bonds when rotations in chloroform are compared with those in other solvents (Table IV). This effect can also be seen from analysis of the recorded literature values

TABLE IV.

| Substance. | $\Delta$ values for reduction of $\Delta^5$ double bond. Acetone. | Alcohol. | Chloroform. | Dioxan. |
|---|---|---|---|---|
| Cholesterol | +229 | +229 | +243 (+251 *) | +228 |
| Dehydro*iso*androsterone | — | +245 | +255 | — |
| Cholesteryl acetate | +223 | +219 | +248 (+243 *) | +232 |
| Dehydro*iso*androsterone acetate | — | +229 | +252 | — |

* Mean values from analysis of literature (see Part II).

in the bile acid and steroidal hormone fields, but space restrictions do not justify such detailed considerations here. In general the $\Delta$ values for this reduction in the steroidal hormone and bile acid fields are those which can be predicted from Table IV. Anomalous cases, for this transformation, are comparatively few and most are included in references 6 and 48 (cf. above). In view of the wide recording of sterol rotations in chloroform solution it is generally desirable that this solvent should be used for the other types of steroid as well in order that comparison between compounds may be facilitated.

It is possible to compile lists of $\Delta$ values for numerous other transformations in the bile acid and steroidal hormone series, but such catalogues serve only to illustrate already enunciated principles and the chemical interest of the subject matter does not justify the mere presentation of lists of substances with anomalous rotatory power. The verification of the incorrectness of the rotations of the substances detailed in Table III will suffice to confirm the validity of the molecular rotation difference method in this field, and other anomalous cases can be corrected by individual workers as the preparation of such compounds is repeated. In any case it is a simple matter to make correlations on the particular molecular change in which one is interested. One generalisation is, however, worth mentioning, *viz.*, that with few exceptions there is practically no difference between the molecular rotations of bile acids and their esters. This is in agreement with the general position in the triterpenoid field (cf. Barton and Jones, *J.*, 1944, 659).

The problem of the formulation of the various derivatives of *u*-ergostanol first described by Windaus and Auhagen (*Annalen*, 1929, **472**, 185) is easily solved by the use of molecular rotation data. That *u*-ergostanol itself is *epi*coproergostanol was suggested by Laucht (*Z. physiol. Chem.*, 1937, **246**, 171) although unambiguous proof was not given. The molecular rotation and melting point of *u*-ergostanol (Windaus and Auhagen, *loc. cit.*) are both too high for the interpolated data for *epi*coproergostanol deduced by the Methods of Differences (for melting point considerations see below), whilst for the *epi*coproergostanol of Wetter and Dimroth (*Ber.*, 1937, **70**, 1665) the physical constants recorded are those expected. Saturated derivatives of cholestanol and ergostanol differ from each other by about 20 to 30 in molecular rotation (the cholestanol compounds being the more positive; see Part I, Table I). *u*-Ergostanol acetate and *u*-ergostane are lower in molecular rotation by 28° and 23° respectively than their corresponding *epi*coprosterol homologues. The agreement here and in the difference (23°) between the molecular rotation of Wetter and Dimroth's *epi*coproergostanol and that of *epi*coprosterol is a strong indication that *u*-ergostane is coproergostane and that *u*-ergostanol acetate is *epi*coproergostanol acetate. The original *u*-ergostanol must have been impure and the description (the acetylation of *u*-ergostanol has never been described) of its preparation is in keeping with this view. Furthermore *u*-ergostanol acetate and Wetter and Dimroth's *epi*coproergostanol acetate have the same melting point.

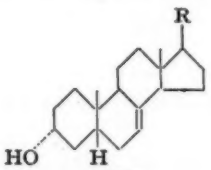
Accepting these identities the formulæ (VII; R = $C_9H_{17}$) and (VIII; R = $C_9H_{17}$, R′ = H) must be assigned to *u*-ergostadienol and to *u*-ergostatrienol respectively. Similarly *u*-ergostatrienol B must be given the formula (IX; R = $C_9H_{17}$, R′ = H) for it absorbs at 2480 A. (Dithmar and Achtermann, *Z. physiol. Chem.*, 1932, **205**, 55) and does not react with maleic anhydride (compare *u*-ergostatrienol which absorbs at 2420 A., and see Part II). The methods of preparation of all these substances are in agreement with these formulations (cf. Windaus, *Annalen*, 1927, **453**, 101, and see Part II). The Δ values for all these compounds are set out in Table V. The

TABLE V.

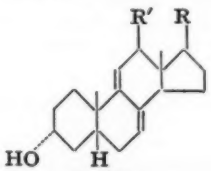
| Substance. | Suggested formula; this paper. | $[M]_D$ in $CHCl_3$. Alcohol. | $[M]_D$ in $CHCl_3$. Acetate. | $\Delta_1$. | $[M]_D$ in $CHCl_3$. Reduced alcohol. | $[M]_D$ in $CHCl_3$. Reduced acetate. | Δ values. Alcohols. | Δ values. Acetates. | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| *u*-Ergostanol ..... | (IV; R = $C_9H_{19}$) | +137 | +178 | + *41* | — | — | — | — | 75, 76, 77 |
| | | +101* | +178 | + *77* | — | — | — | — | |
| *epi*Coprosterol ... | (IV; R = $C_8H_{17}$) | +124 | +206 | + *82* | — | — | — | — | 31 |
| *u*-Ergostadienol ... | (VII; R = $C_9H_{17}$) | +187 | +255 | + *68* | +101* | +178 | −147† | −138† | 75, 76, 77, 78 |
| *u*-Ergostatrienol ... | (VIII; R = $C_9H_{17}$, R′ = H) | +349 | +451 | +*102* | +101 | +178 | −309† | −334† | 75, 76, 77 |
| Coprostadienol D ‡ | (VIII; R = $C_8H_{17}$, R′ = H) | +361 | — | — | +100 | — | −261 | — | 79, 80, 81 |
| *u*-Ergostatrienol B | (IX; R = $C_9H_{17}$, R′ = H) | −194 | −158 | + *36* | +101 | +178 | +234† | +275† | 75, 76, 77 |
| Coprostadienol B ‡ | (IX; R = $C_8H_{17}$, R′ = H) | −184 | −209 | − *25* | +100 | — | +284 | — | 79, 80, 81 |

* As discussed in the text this value, recorded for *epi*coproergostanol, should be identical with that for pure *u*-ergostanol.
† Corrected for side chain reduction (see Reference 93).
‡ These substances have, of course, a 3(β)-ol grouping.

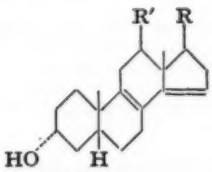
change in Δ value from about +60 in the *allo*cholane series (Part II) to −140 in the cholane series for the reduction of the $\Delta^7$ double bond is particularly remarkable.



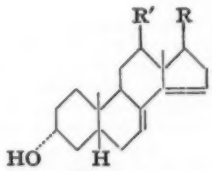
(VII.)



(VIII.)



(IX.)



(X.)

Recently Windaus and Zühlsdorff (*Annalen*, 1938, **536**, 204) have described the thorough characterisation of $\Delta^{6:8(9)}$-coprostadien-3(β)-ol and its rearrangement to coprostadienol B. On the grounds of optical rotation (Table V) this latter substance must now be assigned the formula [IX; R = $C_8H_{17}$, R′ = H and 3(β)-ol] in agreement with its absorption maximum at 2480 A. and its failure to react smoothly with maleic anhydride. A by-product of the treatment of $\Delta^{6:8(9)}$-coprostadienol-3(β)-ol with maleic anhydride was a diene alcohol, m. p. 128—129°, absorbing at 2400 A. The optical rotation (Table V) clearly shows, in agreement with the absorption maximum, that this substance should be called coprostadienol D and be formulated as [VIII; R = $C_8H_{17}$, R′ = H and 3(β)-ol].

The literature contains descriptions of a large number of mono-unsaturated bile acid derivatives. All those that can be treated by the Method of Molecular Rotation Differences are recorded in Table VI and it is possible by this procedure to effect a reduction in the number of substances worthy of consideration as homogeneous entities. In the *allo*cholane series the only double bond position in the molecule which resists catalytic reduction in acetic acid solution at room temperature is at $\Delta^{8(14)}$. Double bonds in other parts of the molecule are either reduced under these conditions or isomerised to the $\Delta^{8(14)}$ compounds. In the cholane series the situation is somewhat different in that $\Delta^7$ compounds seem to be rearranged only sluggishly to the $\Delta^{8(14)}$ isomers by this procedure. Thus among the cholenic acids three are recorded (β-, γ-, and δ-cholenic acids) which resist hydrogenation with either platinum or palladium catalysts, whilst two similar lithocholic and three deoxycholic acid derivatives are reported (see Table VI). β-, γ-, and δ-Cholenic acids have Δ values for the reduction of the double bond of from −56° to −75°, and are best regarded as mixtures of $\Delta^7$ and $\Delta^{8(14)}$ acids. The other possible position of the double bond at $\Delta^{8(9)}$ is most unlikely, for Windaus and Zühlsdorff (*loc. cit.*) have shown that δ-coprostenol (for Δ value see Table VI) is smoothly rearranged by hydrogenating catalysts, as is δ-cholestenol, to give the α-isomer (double bond shift from $\Delta^{8(9)}$ to $\Delta^{8(14)}$). The Δ value for the reduction of the double bond in α-coprostenol cannot be obtained by direct comparison, but by deduction from the recorded values for the molecular rotations of the acetate and dinitrobenzoate it is clear that practically no change in rotation is caused by this transformation. The cholenic acids under consideration, therefore, are mixtures of ⅓ to ½ of the $\Delta^7$ isomer with ⅔ to ½ of the $\Delta^{8(14)}$ isomer. Although the *apo*chenodeoxycholic acids (Takahashi, *Z. physiol. Chem.*, 1938, **255**, 277; Yamasaki and Takahashi, *ibid.*, 1938, **256**, 21) differ in melting point it seems that both are mainly the $\Delta^7$ isomer. The formulation of *apo*cholic and β-*apo*cholic acids is specially interesting. For chemical reasons summarised by Callow (*J.*, 1936, 462) *apo*cholic acid must be

TABLE VI.

| Substance. | ⊨ position: literature. | ⊨ position: this paper. | Solvent. | $[M]_D$. Unsaturated acid. | $[M]_D$. Saturated acid. | Δ (in cholane series). | Δ (in *allo*-cholane series). | References. |
|---|---|---|---|---|---|---|---|---|
| $\Delta^2$-Cholenic acid ..... | 2 : 3 | 2 : 3 | $C_2H_5OH$ | + 61 | +102† | + 41 | −152 | 83, 84, 85 |
| $\Delta^3$-Cholenic acid ..... | 3 : 4 | 3 : 4 | $C_2H_5OH$ | + 68 | +102 | + 34 | — | 83, 84, 85 |
| $\Delta^5$-Cholenic acid ..... | 5 : 6 | 5 : 6 | $C_2H_5OH$ | −240 | +102 | +342 | +296 | 83, 84, 85 |
| β-Cholenic acid ‡ ..... | 8 : 14 | Mixed 7 : 8 and 8 : 14 | $CHCl_3$ | +140 | + 79 | − 61 | — | 84, 85, 86 |
| γ-Cholenic acid ‡ ..... | — | | $CHCl_3$ | +154 | + 79 | − 75 | — | 84, 85, 87 |
| δ-Cholenic acid ‡ ..... | 8 : 14§ | | $C_2H_5OH$ | +158 | +102 | − 56 | — | 84, 85, 88 |
| *apo*Chenodeoxycholic acid ‡ ..... | 8 : 14 | Mainly 7 : 8 | $C_2H_5OH$ | +266 | +128 | −138 | + 77 ‖ | 32, 72, 73, 86 |
| β-*apo*Chenodeoxycholic acid ‡ ..... | 8 : 14§ | | $C_2H_5OH$ | +288 | +128 | −160 | + 77 ‖ | 32, 72, 73, 88 |
| *apo*Cholic acid ‡ ..... | 8 : 9 or 8 : 14 | 8 : 14 | $C_2H_5OH$ | +183 | +220 | + 37 | + 9 ‖ | 89, 90, 91, 92, 93, 94, 95 |
| β-*apo*Cholic acid ‡ ..... | 8 : 14§ | 7 : 8 | $C_2H_5OH$ | +308 | +220 | − 88 | + 77 ‖ | 89, 96 |
| Dihydroxycholenic acid... | 7 : 8 or 14 : 15 | 14 : 15 | $C_2H_5OH$ | +238 | +220 | − 18 | − 24 ‖ | 89, 91, 94, 95, 96, 97, 98, 99 |
| *iso*Dihydroxycholenic acid ‡ ..... | 8 : 9 | Rearrangement | $C_2H_5OH$ | + 23 | +220 | +197 | — | 89, 95, 98, 99, 100 |
| 3(α)-Bile acids (cholane * series) ..... | 9 : 11 | 9 : 11 | All | — | — | − 48 | −100 ‖ | 32, 36, 71, 72, 73, 74 |
| 3(α)-Bile acids (cholane * series) ..... | 11 : 12 | 11 : 12 | All | — | — | − 26 | — | 26, 27, 30, 32, 36, 71, 72, 73 |
| 3 : 7 : 22-Trihydroxy-$\Delta^{14}$-cholene ..... | 14 : 15 | 14 : 15 | $C_2H_5OH$ | +128 | +121 | − 7 | − 24 ‖ | 101 |
| δ-Coprostenol ..... | 8 : 9 | 8 : 9 | $CHCl_3$ | + 58 | +100 | + 42 | + 48 ‖ | 79, 80, 81 |

* Three examples, in good agreement with each other, are available in both series (see References cited).
† This rotation is assigned from a knowledge of the rotation in $CHCl_3$ (compare Reference 33).
‡ These substances resist catalytic hydrogenation.
§ With $C_9$ epimerism.
‖ These values apply to the corresponding 3(β)-ol compounds, but will not be very different from the true Δ values for the analogous 3(α)-ol substances.

either $\Delta^{8(9)}$ or $\Delta^{8(14)}$. The failure of *apo*cholic acid to rearrange under the influence of hydrogenating catalysts in acetic acid solution is a clear confirmation of the views of Callow (*loc. cit.*) that it has a $\Delta^{8(14)}$ bond. Optical rotatory power evidence (cf. Callow and Young, *Proc. Roy. Soc.*, 1936, *A*, **157**, 194) is not in disagreement with this formulation, but clearly shows in addition that β-*apo*cholic acid is substantially the $\Delta^7$ isomer (compare Tables V and VI) and not the $C_9$ epimer of normal *apo*cholic acid as suggested by Callow (*loc. cit.*). It is clear also that the formulation of dihydroxycholenic acid as the $\Delta^{14}$ analogue of *apo*cholic acid is correct. Thus chemical evidence shows that dihydroxycholenic acid must be either $\Delta^7$ or $\Delta^{14}$ unsaturated, but optical evidence (Table VI) as well as the facile catalytic reduction of this substance prove that the $\Delta^7$ bond cannot be present in spite of the persistent formulations of Japanese workers to this effect (see, *e.g.*, papers in *J. Biochem. Japan*, 1939, etc.). *iso*Dihydroxycholenic acid is unique amongst the isomers of *apo*cholic acid in having a large positive Δ value on reduction (assuming a relationship to deoxycholic acid) and it is impossible to reconcile this with any double bond position in the cholane skeleton (Table VI). Previously the most logical formulation for this acid was as the $\Delta^{8(9)}$ isomer, but a comparison with δ-coprostenol precludes this position. *iso*Dihydroxycholenic acid, moreover, is not rearranged to *apo*cholic acid under hydrogenating conditions, or by hydrogen chloride or light. Its reaction with bromine is likewise peculiar. It is to be concluded that *iso*dihydroxycholenic acid is formed by some rearrangement of the *apo*cholic acid molecule and that its catalytic perhydrogenation will not be found to yield deoxycholic acid.

The conjugated dihydroxycholadienic acids, derived by the action of oxidising agents on α-*apo*cholic acid and on dihydroxycholenic acid (cf. Borsche and Todd, *Z. physiol. Chem.*, 1931, **197**, 173), have been formulated by Callow (*loc. cit.*) as (X; R = $C_5H_9O_2$, R′ = OH) for the α-acid and as (IX; R = $C_5H_9O_2$, R′ = OH) for the β-acid. The chemical and physical evidence with regard to these two acids is not in agreement throughout but a study of optical rotatory power (Table VII) and other facts makes it clear that these two formulations

TABLE VII.

| Substance. | ⊨ positions: literature. | ⊨ positions: this paper. | Solvent. | $[M]_D$. Unsaturated acid. | $[M]_D$. Saturated acid. | Δ. | Refs. |
|---|---|---|---|---|---|---|---|
| α-Dihydroxycholadienic acid ... | 7 : 8, 14 : 15 | 8 : 9, 14 : 15 | Alcohol | −241 | +220 | +461 | 89, 96 |
| β-Dihydroxycholadienic acid ... | 8 : 9, 14 : 15 | 7 : 8, 14 : 15 | Alcohol | +303 | +220 | − 83 | 89, 96 |

of Callow cannot be correct. The Δ value for α-dihydroxycholadienic acid is comparable with that for coprostadienol B and for *epi*coproergostadienol B (see Table V above); it must be reformulated, therefore, as

(IX; R = $C_5H_9O_2$, R′ = OH). The positively rotatory β-dihydroxycholadienic acid, on the other hand, is best formulated as (X; R = $C_5H_9O_2$, R′ = OH) in agreement with its reduction to β-*apo*cholic acid (see above).

*Note on the use of Melting Point Differences in the Steroid Field.*—If the same principles which lead to the additivity of the Δ values of molecular rotations were decisive in determining the temperature of fusion of organic compounds in general, and of steroids in particular, then a similar "Method of Differences" should operate in both cases. Broad generalisations relating melting point to structure are unknown, but it does seem possible to observe some regularities in the comparative melting points of a group of closely related substances such as the sterols. Thus for saturated sterols with rings A and B in the *cis*- or *trans*-position and with the 3-hydroxyl in the (β) or (α) orientation there are comparable differences in melting point between corresponding pairs of isomers in the cholestane and the β-sitostane series. The same applies in the ergostane series too, if the melting point of *epi*coproergostanol is taken as about 130°, but not if taken as 184° (the melting point of *u*-ergostanol). On the other hand the melting point for *u*-ergostanyl acetate is in agreement (as is its Δ value, see above) with that expected. These facts support the suggested inhomogeneity of *u*-ergostanol mentioned earlier in this paper.

An interesting fact about the melting points of simple sterols [of the 3(β)-ol type] is that all have higher melting points than their acetates except those which have been assigned a $\Delta^7$ bond on optical rotation evidence in Parts I and II. When a $\Delta^7$ bond is present in the molecules the acetates melt at a higher temperature than the parent sterols. This exceptional behaviour can be used in assigning a nuclear double bond position to the mixed stellasterols (see Bergmann and Stansbury, *J. Org. Chem.*, 1944, **9**, 281). These mixed sterols resist separation, and the nuclear double bond present cannot be hydrogenated catalytically. The $\Delta_1$ value for the mixed sterols is − 23° and the $\Delta_2$ value + 13°. An inspection of Table III, Part I, shows that these differences correspond only to a $\Delta^7$ or $\Delta^{14}$ double bond position, the latter being eliminated on chemical grounds. The $\Delta^7$ formulation is supported by the report that the melting point of the mixed acetates is greater than that of the parent sterols. It is predicted, therefore, that the mixed stellasterols all have a $\Delta^7$ nuclear double bond and differ from each other only in side chain configuration and/or unsaturation—probably the latter.

Further points of interest are that the melting points of α-stenols of the 3(β)-*trans*-configuration are always

TABLE VIII.

| Substance. | Solvent. | $[\alpha]_D$ (to nearest degree). | *c* (g. per 100 ml.). | *l* (dm.). | $[M]_D$. |
|---|---|---|---|---|---|
| Cholesterol | Acetone | −28 | 1·08 | 1 | −116 |
| | Acetone | −32 | 1·20 | 2 | |
| | Alcohol | −27 | 1·17 | 1 | −116 |
| | Alcohol | −33 | 0·59 | 1 | |
| | Alcohol | −30 | 1·00 | 2 | |
| | Chloroform | −40 * | 2·00 | 1, 2 | −154 |
| | Dioxan | −34 | 2·16 | 1 | −131 |
| Cholesteryl acetate | Acetone | −33 | 2·03 | 1 | −141 |
| | Acetone | −33 | 1·44 | 2 | |
| | Acetone | −32 | 0·58 | 2 | |
| | Alcohol | −30 | 0·72 | 1 | −137 |
| | Alcohol | −34 | 1·25 | 2 | |
| | Chloroform | −44 * | 2·00 | 1, 2 | −188 |
| | Dioxan | −38 | 1·93 | 1 | −163 |
| Cholestanol | Acetone | +29 | 1·65 | 2 | +113 |
| | Alcohol | +29 | 1·24 | 2 | +113 |
| | Chloroform | +23 * | 2·00 | 1, 2 | + 89 |
| | Dioxan | +25 | 1·78 | 1 | + 97 |
| Cholestanyl acetate | Acetone | +19 | 0·72 | 2 | + 82 |
| | Alcohol | +19 | 0·85 | 2 | + 82 |
| | Chloroform | +14 * | 2·00 | 1, 2 | + 60 |
| | Dioxan | +15 | 2·08 | 1 | + 69 |
| | Dioxan | +16 | 2·86 | 1 | |
| Dehydro*iso*androsterone | Alcohol | +13 | 3·22 | 1 | + 37 |
| | Alcohol | +12 | 1·29 | 2 | |
| | Chloroform | + 2 * | 2·00 | 1, 2 | + 6 |
| Dehydro*iso*androsterone acetate | Alcohol | + 6 | 2·04 | 2 | + 20 |
| | Chloroform | − 7 * | 2·00 | 1, 2 | − 23 |
| *iso*Androsterone | Alcohol | +95 | 2·21 | 1 | +276 |
| | Alcohol | +95 | 0·88 | 2 | |
| | Chloroform | +90 | 3·16 | 1 | +261 |
| | Chloroform | +90 | 1·26 | 2 | |
| *iso*Androsterone acetate | Alcohol | +76 | 1·84 | 1 | +249 |
| | Alcohol | +74 | 0·74 | 2 | |
| | Chloroform | +69 | 1·84 | 1 | +229 |
| | Chloroform | +68 | 0·74 | 2 | |

* These values are obtained from interpolation of a whole series of specific rotations obtained from *c* = 1 upwards. The change of rotation with concentration is small.

below those of any other isomer with nuclear unsaturation and that the $\Delta^4$-3-ketones obtained by oxidising $\Delta^5$-stenols are very much lower in melting point than the parent stenols, whereas when the double bond is in a different position in the nucleus no great change in melting point is observed on transformation to the ketone.

Although generalisations of this type can be made and are useful, there are many irregularities. A consideration of melting points can never yield the valuable results that optical rotatory power can, because the melting point is a function of both intra- and inter-molecular forces, whereas optical rotatory power is, in solution, mainly a manifestation of intramolecular forces only. Nevertheless a comparative examination of melting points should not be neglected in sterol work particularly when dealing with naturally occurring products.

## Experimental.

All rotations were taken at 24° ± 2° and for the $Na_D$ line, using a 1 or 2 dm. macro-tube. All substances examined were purified as carefully as possible before use and dried in a vacuum at 20° below their melting points. M. ps. are uncorrected. Cholesterol, m. p. 148·5°. Cholesteryl acetate, m. p. 114·5°. Cholestanol, m. p. 142·5°. Cholestanyl acetate (from cholesteryl acetate by catalytic reduction in acetic solution with platinum oxide catalyst), m. p. 110°. Dehydro-*iso*androsterone, m. p. 148°. Dehydro*iso*androsterone acetate, m. p. 172°. *iso*Androsterone, m. p. 174°. *iso*Androsterone acetate (from dehydro*iso*androsterone acetate by the method of Reichstein and Lardon, *Helv. Chim. Acta*, 1941, **24**, 955), m. p. 105°.

For the determinations of the rotations of cholesterol and its derivatives in alcohol and acetone, 2% by volume of chloroform was added to increase the solubility. Preliminary experiments showed that this small addition of chloroform had no appreciable influence on the optical rotations observed.

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## 249. *The Difluoroarsines.*

By L. H. LONG, H. J. EMELÉUS, and H. V. A. BRISCOE.

*Methyl-* and *ethyl-difluoroarsine* have been completely identified and their more important physical and chemical properties described. They are liquids boiling at 76·5° and 94·3° respectively. The solid *phenyl-difluoroarsine* and the liquid 2-chlorovinyldifluoroarsine have also been characterised. The method employed for the preparation of difluoroarsines was to treat the corresponding dichloroarsines with anhydrous ammonium fluoride at 80—100°. This fluoride will also fluorinate dimethylchloroarsine, and is recommended as a very convenient agent for the general preparation of fluorine-substituted arsines from the chloro-compounds. The fluorination is normally smooth and the yields are almost quantitative.

APART from dimethylfluoroarsine, $AsMe_2F$, described by Bunsen (*Annalen*, 1841, **37**, 38) there are no data concerning any of the alkylfluoroarsines. For the preparation of the alkyldifluoroarsines four lines of attack are possible, namely: (i) from the corresponding chlorides, bromides, or iodides; (ii) replacement of halogen by fluorine in, *e.g.*, $AsMe_2Cl_3$, the required substance being obtained by thermal decomposition of the primary product, $AsMe_2F_3 \longrightarrow AsMeF_2 + MeF$, by analogy with the chlorine compound; (iii) the action of hydrogen fluoride on the corresponding alkylarsenine oxide, $AsRO + 2HF \longrightarrow AsRF_2 + H_2O$; (iv) addition of a suitable alkylmagnesium halide to excess of arsenic trifluoride, $AsF_3 + MgRI \longrightarrow AsRF_2 + MgIF$. Method (i) was adopted as being the most suited to laboratory preparation. The starting materials were methyl- and ethyl-dichloroarsine, prepared as outlined below.

### EXPERIMENTAL.

*Preparation of the Alkyldichloroarsines.*—(i) *Methyldichloroarsine.* The method employed was essentially the same as the industrial method described by Uhlinger and Cook (*J. Ind. Eng. Chem.*, 1919, **11**, 105) but modified somewhat in the later stages to avoid an awkward steam-distillation and provide a more satisfactory yield on the scale usually carried out in the laboratory. After the production of sodium methylarsinate in the reaction $Na_3AsO_3 + Me_2SO_4 \longrightarrow AsMeO(ONa)_2 + NaMeSO_4$, methyl alcohol formed by hydrolysis is distilled off at 100°. A small quantity of potassium iodide is added and the solution neutralised with sulphuric acid. The cold solution is mixed with an equal volume of fuming hydrochloric acid, rapidly filtered, and reduced with a stream of sulphur dioxide until no more oil separates: $AsMeO(OH)_2 + 2HCl + SO_2 \longrightarrow AsMeCl_2 + H_2SO_4 + H_2O$. The methyldichloroarsine is run off, dried, and fractionated under atmospheric pressure (b. p. 132—133°; yield 30—50%, depending chiefly on the success of the initial methylation).

(ii) *Ethyldichloroarsine.* This preparation was carried out in a similar manner, except that the alkylating agent employed was ethyl iodide. The latter compound is refluxed with sodium arsenite solution under continuous stirring until no more ethyl iodide is absorbed: $Na_3AsO_3 + EtI \longrightarrow AsEtO(ONa)_2 + NaI$. Before acidification and reduction as in the previous preparation, the bulk of the sodium iodide is removed by adding methyl sulphate and distilling off the methyl iodide formed. The final fractionation of the ethyldichloroarsine is conducted under reduced pressure (for vapour-pressure data, see Gibson and Johnson, *J.*, 1931, 2520); yield 60—65%.

*Preparation of Alkyldifluoroarsines.*—The substance found to be most suitable for the replacement of the chlorine in dichloroarsines was anhydrous ammonium fluoride, which effects the conversion at 80° in almost quantitative yield, whereas antimony trifluoride, with or without a catalyst, and zinc fluoride are without action at 100°. A fair excess of ammonium salt is to be recommended, as otherwise the reaction tends to become very slow as it approaches completion. The difluoroarsine may be removed as it is formed by continuous fractionation. The following is a description of the procedure finally adopted for the conversion of methyl- and ethyl-dichloroarsines.

Crystalline ammonium fluoride (3 mols.), dried thoroughly in a vacuum desiccator, and pure methyldichloroarsine (1 mol.) are placed in a "Pyrex" Kon fractionating flask, the system being protected from atmospheric moisture by a calcium chloride guard-tube. The flask is heated in a water-bath to 70° and then more slowly to 90°. Reaction sets in a little below 80° as is seen by the loss of crystalline appearance of the ammonium fluoride. When the temperature of the bath reaches about 90° distillation commences, the temperature at the head of the column registering 76—77°. The distillation is complete in 2—3 hours. The temperature at the head of the column must not exceed 78° or the product becomes contaminated with chloro-compound. The product is refractionated and distils constantly at 76·5°.

With slight modification the same procedure can be adopted with ethyldichloroarsine. Since ethyldifluoroarsine boils at 94° the reaction is best carried out under a somewhat reduced pressure, *e.g.*, 400 mm., at which the b. p. is 74°. Alternatively an oil-bath at 110—120° may be employed, but the former method is to be preferred since chemical attack on the flask increases with temperature. "Pyrex" flasks are only slightly etched below 100° in either preparation.

90—95% Yields of *methyl-* and *ethyl-difluoroarsines* can be obtained in this manner without difficulty. It is not advisable to crush the ammonium fluoride finely beforehand as this causes the reaction to set in somewhat vigorously and the product is contaminated with unchanged dichloroarsine. Since there is a slow but definite attack on glass, the difluoroarsines cannot be kept in glass bottles, but should be stored in platinum, copper, or lead. Both compounds are solid at −80°, and at this temperature there is no noticeable action on glass.

*Characterisation of the Alkyldifluoroarsines.*—The methyl and the ethyl compound on hydrolysis yield the corresponding oxides, which possess very characteristic unpleasant odours resembling that of asafœtida. The hydrolysis products of the difluoroarsines possess these typical smells, indistinguishable from those produced by hydrolysing the corresponding dichloroarsines. The methyl oxide (AsMeO) produced by hydrolysis of methyldifluoroarsine was identified by oxidation

with sodium peroxide to sodium methylarsonate, $AsMeO(ONa)_2$. This substance is known to evolve methane when heated with sodium hydroxide (Auger, *Compt. rend.*, 1908, **146**, 1280). The salt was obtained by evaporation and fused in an evacuated tube connected with a Töpler pump. The gas evolved was passed at low pressure through a U-tube cooled in liquid nitrogen and collected in the reservoir of the Töpler pump; it was odourless, and when ignited, burnt with a faintly luminous flame. The mass left after fusion was shown by qualitative tests to contain sodium arsenate: $AsMeO(ONa)_2 + NaOH \longrightarrow Na_3AsO_4 + CH_4$.

The quantitative analysis of methyldifluoroarsine was carried out by two independent methods, one gravimetric and one volumetric. The first involved hydrolysis of a known amount, conversion of the combined arsenic present into arsenate, and estimation of this as silver salt (Sarudi, *Z. anal. Chem.*, 1938, **113**, 248). After removal of excess silver as oxide, the fluorine present was estimated as calcium fluoride (Hillebrand and Lundell, "Applied Inorganic Analysis," 1929, p. 802). The procedure was carried out in platinum apparatus except for the weighing of the difluoroarsine which was done in small "Pyrex" ampoules. A small error was hereby introduced owing to the formation of a trace of silicon fluoride (Found: As, 57·15, 57·51, 57·45; F, 30·64, 28·95, 30·21. $CH_3AsF_2$ requires As, 58·55; F, 29·70%).

An attempt was made to estimate the percentage of methyl radical by measuring the volume of methane formed in the conversion of methylarsonate into arsenate: Auger (*loc. cit.*) states that the production of methane at 250° is quantitative. This proved to be difficult, since the presence of relatively large amounts of sodium fluoride and carbonate, formed by absorption of atmospheric carbon dioxide during evaporation, prevented complete fusion, and even when the temperature was raised somewhat, several hours elapsed before the evolution of methane was completed. The value for methyl in methyldifluoroarsine was estimated as 11·67% (Calc.: 11·75%). Against this, however, a rather high "blank" determination carried out on the sodium peroxide and hydroxide used must be considered, which reduces the experimental figure to about 11·4%.

The second method for the estimation of arsenic and fluorine, used by Uhlinger and Cook (*loc. cit.*, p. 108), involved hydrolysing a known amount of substance and titrating the solution formed, first with alkali to determine the hydrogen fluoride, and secondly with iodine to determine the tervalent arsenic. The following results were obtained: For $AsMeF_2$: Found: As, 58·21, 58·50, 58·46; F, 29·56, 29·74, 29·76 ($CH_3AsF_2$ requires As, 58·55; F, 29·70%). For $AsEtF_2$: Found: As, 52·70, 52·75, 52·62; F, 26·93, 26·81, 26·87 ($C_2H_5AsF_2$ requires As, 52·77; F, 26·77%).

*Physical Properties of the Alkyldifluoroarsines.*—Methyl- and ethyl-difluoroarsines are colourless, mobile liquids. The vapours possess powerful, irritating smells, and resemble those of the alkyl dichloroarsines in their aggressiveness. There is a tendency to fume in moist air, a property not shared by the dichloroarsines.

*Vapour pressure.* The compound was distilled into a small bulb connected with a mercury manometer. The bulb was surrounded by a large acetone–carbon dioxide bath kept well stirred, and the pressures recorded for a series of temperatures. To avoid error due to the formation of traces of silicon fluoride, a tap connecting the bulb to an evacuating pump was momentarily opened immediately before the taking of a reading, and the pressure noted as soon as equilibrium was re-established. The temperature was measured by a sulphur dioxide vapour-pressure thermometer over the range below −10°, and by a standardised mercury thermometer at higher temperatures.

Above room temperature it was impossible to determine the vapour pressure accurately in a closed Stock vapour-pressure bulb owing to formation of silicon tetrafluoride, which becomes more rapid as the temperature increases. Resort had therefore to be made to distillation under reduced pressure. The usual temperature corrections for the mercury manometer and exposed thermometer stem were applied throughout. The experimental data are tabulated below. In neither case is the relation between the logarithm of the pressure and the reciprocal of the absolute temperature truly linear. A second term involving $T$ has therefore been introduced into the derived equations.

*Experimental data for methyldifluoroarsine.*

| Temp. | −29·0° | −21·3° | −15·1° | −10·1° | − 4·6° | + 0·1° | 4·5° | 9·0° | 13·7° |
|---|---|---|---|---|---|---|---|---|---|
| $p$ (mm.) | 3·0 | 5·5 | 8·0 | 11·5 | 16·5 | 22·0 | 29·0 | 37·5 | 48·5 |
| Temp. | 18·0° | 23·3° | 28·4° | 36·1° | 45·2° | 54·2° | 63·3° | 71·2° | 77·0° |
| $p$ (mm.) | 61·5 | 80·0 | 103·5 | 143 | 225 | 330 | 475 | 632 | 772 |

These data are represented by the equation $\log p_{mm.} = 7{\cdot}5315 - 1399/T - 79{,}400/T^2$. The vapour pressure reaches 760 mm. at 76·5°.

*Experimental data for ethyldifluoroarsine.*

| Temp. | −25·5° | −17·0° | −10·3° | − 4·3° | + 0·8° | 5·6° | 10·3° | 15·3° | 20·3° | 24·9° |
|---|---|---|---|---|---|---|---|---|---|---|
| $p$ (mm.) | 2·0 | 3·5 | 5·5 | 8·5 | 11·5 | 15·0 | 20·0 | 26·5 | 34·5 | 44·0 |
| Temp. | 31·9° | 39·5° | 46·8° | 53·3° | 60·1° | 67·2° | 75·4° | 83·2° | 91·0° | 94·6° |
| $p$ (mm.) | 63 | 94 | 130 | 178 | 236 | 305 | 412 | 546 | 678 | 767 |

The following vapour-pressure equation has been deduced: $\log p_{mm.} = 6{\cdot}0960 - 590/T - 217{,}100/T^2$. The vapour pressure reaches 760 mm. at 94·3°.

*Melting point.* The melting point of the ethyl compound was very sharp, the values obtained being −38·7°, −38·9°, −38·7°, −38·6°, −38·6° (mean −38·7°). The methyl compound, however, even after repeated fractionations in vacuum apparatus, melted over a range of 1·0—1·5°, and the temperature of initial melting was recorded. The following experimental values were obtained: −29·8°, −29·6°, −29·7°, −29·7°, −29·8° (mean −29·7°).

*Liquid density.* For the determination of liquid density, use was made of a capillary tube of even bore with a suitable-sized bulb blown at one end. This was calibrated with pure benzene and with water. The difluoroarsines were distilled in a vacuum into the bulbs, which were attached to vacuum apparatus by means of ground glass joints. The bulbs were subsequently sealed off. The measurements were made in a large Dewar flask with an unsilvered strip down one side to enable the necessary cathetometer observations to be made. The temperature of the bath was accurately measured by a vapour-pressure thermometer or a standardised mercury thermometer. Measurements were made between −30° and +35°. Above the latter temperature there was a noticeable etching of the inside of the glass bulb. For the methyl compound the density at $t$° c. is given by the expression: $d_t = 1{\cdot}972 - 0{\cdot}00267t$. A check determination on a fresh sample furnished a value of 1·924 at 18·4°. The mean coefficient of expansion is 0·00138. For the ethyl compound the density relation calculated from experimental figures (−28·7° to 33·3°) is $d_t = 1{\cdot}743 - 0{\cdot}00217t$. A separate determination gave a value of 1·708 at 17·0°. The mean coefficient of expansion is 0·00128.

A point of interest is that the liquid densities of the difluoroarsines are considerably higher than those of the corresponding dichloroarsines, a fact which possibly indicates association in the liquid phase. It will be shown later that other considerations point to the same conclusion.

*Vapour density.* This was the most difficult physical property to determine. The measurements obviously could not be conducted in glass. The method adopted involved the use of an all-platinum vessel of nearly 300 ml. capacity,

which had been employed for the determination of the vapour density of hydrogen fluoride (Thorpe, *J.*, 1889, **55**, 163). A suitable quantity of substance was distilled into the evacuated bulb and the increase in weight noted. One of the platinum cocks was connected by a short piece of thick rubber tubing to a U-tube constructed of 1-mm. capillary tubing containing a quantity of mercury. The limb of the U-tube connected to the vapour-density bulb was about 10 cm. long. The other limb was much longer and was connected to an evacuating pump. The short limb was provided with a small bulb near the base to act as a mercury reservoir. The small space above the mercury in the short limb could be separately evacuated. The platinum bulb and the base of the U-tube, including the whole of the short limb, were immersed in a large water-bath which was kept at boiling temperature. Both sides of the U-tube having been evacuated, the platinum cock connecting it to the bulb was opened. By the admission of a regulated quantity of air into the tubing sealed on to the long limb, the pressures on each side of the U-tube were approximately equalised. In less than 2 minutes equilibrium was established. The pressure in the bulb was determined immediately by measuring the pressure the other side of the U-tube on a manometer and correcting for the small difference in mercury levels in the two limbs of the U-tube, determined by the help of a glass scale fixed to the back of the U-tube. To minimise error due to difference in surface tension in the two limbs of the capillary U-tube, both sides of the tube were re-evacuated, and any difference in the levels of the mercury noted. The volume of the bulb and that of the short length of capillary tubing included in the system were accurately known. The vapour density at the boiling point of water could therefore be calculated, and from this the molecular weight (Calc. for $CH_3AsF_2$: 127·94; for $C_2H_5AsF_2$: 141·97).

| | *Experimental data for methyldifluoroarsine.* | | | *Experimental data for ethyldifluoroarsine.* | | |
|---|---|---|---|---|---|---|
| Temp. | 100·5° | 100·3° | 100·3° | 99·5° | 99·7° | 99·6° |
| Pressure, mm. | 420 | 369 | 308 | 428 | 320 | 253 |
| Mol. wt. | 175 | 172 | 167 | 170 | 162 | 159 |

These experimental data show that there is a certain amount of association in the vapour phase at 100°, especially with the methyl compound.

*Latent heat of vaporisation.* The latent heat of vaporisation ($L_{b.p.}$) has been calculated for each compound from the vapour pressure equation. For the methyl compound, $L$ = 8480 cals./g.-mol. or 66·3 cals./g., and for the ethyl compound, 8110 cals./g.-mol. or 57·1 cals./g. The fact that $L$ per g.-mol. is greater in the case of the methyl compound may be explained by a higher degree of association in the liquid phase. From these values for $L$, the values of Trouton's constant have been calculated as 24·3 and 22·1, respectively. The value for the ethyl compound is only slightly above the mean figure for unassociated compounds, but that for the methyl compound is well above and gives strong indication of association.

*Chemical Properties of the Alkyldifluoroarsines.*—In most of their reactions the difluoro- resemble the dichloro-arsines. For instance, with water or aqueous alkali the corresponding alkylarsenine oxide is formed. The difluoroarsines are readily oxidised. Concentrated nitric acid reacts vigorously in the cold with evolution of oxides of nitrogen. Oxidation also occurs, but less violently, with bleaching powder, bromine water, and hydrogen peroxide. Oxidation will take place with iodine solution in the presence of alkali. The primary product of oxidation is the corresponding alkylarsonic acid, $AsRO(OH)_2$, or one of its salts.

One point of difference between the difluoro- and the dichloro-arsines is their behaviour towards concentrated aqueous solutions of the respective hydrogen halides. The dichloroarsines are not appreciably hydrolysed by hydrochloric acid solutions of moderate concentration: in fact, if either of these arsines is hydrolysed by the minimum quantity of water, the original dichloroarsine can be reprecipitated from solution by addition of the concentrated acid. But the difluoroarsines, once hydrolysed, cannot be reprecipitated by the addition of 40% hydrofluoric acid, although the resulting solution smells strongly of the difluoroarsine. This may be due partly to the associated difluoroarsines having a higher solubility in water, and partly to the fact that hydrofluoric is a much weaker acid than hydrochloric. Thus the difluoroarsines cannot be prepared by the action of hydrofluoric acid on the alkylarsenine oxides, in accordance with the method employed for the production of the dichloroarsines; they can, however, be prepared by distilling anhydrous AsMeO or AsEtO with a mixture of concentrated sulphuric acid and calcium fluoride.

The difluoroarsines etch glass, producing silicon tetrafluoride. When the compounds are pure and dry the attack is very slow. Pyrex is less affected than soda glass. They do not react with such metals as copper and lead in the cold.

*Phenyldifluoroarsine.*—Pure phenyldichloroarsine was heated in a distilling flask with a large excess of anhydrous ammonium fluoride for 2 hours at 100° with exclusion of moisture. Subsequently the pressure was reduced to about 12 mm., and the product distilled off through a short air condenser and twice refractionated. At 48 mm. pressure it distilled constantly at 110°. The final product was a white crystalline solid with a waxy appearance (m. p. 42°). It fumed in moist air, possessed an irritating smell resembling that of the initial chlorine compound, and was very deliquescent. It etched glass slightly.

A little of the solid was hydrolysed with water, and the hydrolysis products shown to contain fluoride but no chloride ions. One of the products was a white solid insoluble in water, but soluble in sodium hydroxide solution and reprecipitated by dilute acids; it was identified as phenylarsenine oxide by a mixed m. p. determination with authentic oxide produced by hydrolysis of the dichloroarsine. This confirms that the new compound is the anticipated *phenyldifluoroarsine*, $AsPhF_2$. As a quantitative check, some of the solid was crushed and transferred to a weighing bottle as quickly as possible. Small quantities were accurately weighed out and treated with a large volume of water. A known volume of standardised sodium hydroxide solution was added to each portion. As soon as hydrolysis was completed, the amount of hydrogen fluoride liberated was determined by titrating the excess of alkali with hydrochloric acid. The tervalent arsenic was subsequently titrated with iodine as in the analysis of the alkyldifluoroarsines. In this case, the presence of a small amount of benzene was necessary to bring the water-insoluble arsine into solution. The end-point, in consequence, was rather more difficult to ascertain with accuracy (Found: As, 38·79, 39·02; F, 19·94, 19·68. $C_6H_5AsF_2$ requires As, 39·43; F, 20·00%).

*2-Chlorovinyldifluoroarsine.*—2-Chlorovinyldichloroarsine similarly reacted with anhydrous ammonium fluoride below 80°, but it was best to heat the reagents in a Kon fractionating flask at 100° under rigid exclusion of moisture for about 1½ hours, using excess of the fluoride. The product could be subsequently distilled off in good yield from a water-bath at a pressure of 75 mm. or lower. If, instead of reducing the pressure, the temperature was raised, decomposition set in just above 140° with production of dense white fumes. The product, on refractionation at a pressure of 14·5 mm., boiled steadily at 43·5°. It was a colourless liquid considerably more volatile than the original arsine. It does not possess the geranium-like odour of the chlorovinyldichloroarsine, but has a highly irritating smell resembling that of the alkyldifluoroarsines. The products of hydrolysis, however, smell persistently of geraniums. The behaviour towards glass is similar to that of the alkyldifluoroarsines.

The solution formed by hydrolysis of some of the substance was neutralised with dilute sodium hydroxide and rendered very faintly acid with acetic acid. On addition of calcium chloride solution, calcium fluoride was precipitated.

No precipitate was formed when the dichloroarsine was similarly treated. Again, on hydrolysing the new compound with dilute nitric acid and adding silver nitrate solution, no trace of silver chloride was precipitated, in contrast to the results of applying this test to the dichloroarsine. This indicated that both of the original hydrolysable chlorine atoms attached to the arsenic atom had been replaced by fluorine atoms. When 2-chlorovinyldichloroarsine is treated with aqueous alkali of sufficient concentration, acetylene is quantitatively evolved. A similar evolution took place when the fluorinated compound was shaken with potassium hydroxide solution, thus confirming the existence of the ·CH:CH· grouping. After acidification of the resulting solution with nitric acid, the production of a copious precipitate with silver nitrate solution demonstrated the presence of chloride ions liberated by the action of the alkali on the chlorovinyl group. The existence of the chlorovinyl group was thus established. This new substance is therefore 2-chlorovinyldifluoroarsine.

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## 250. *The Alkyl- and Aryl-substituted Fluorides of Sulphur, Selenium, Tellurium, and Iodine.*

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A number of new aryl and alkyl fluorides of sulphur, selenium, and tellurium of the type $RXHal_3$, $R_2XHal_2$ and $R_3XHal$ have been prepared and characterised, together with the new *compound* $Ph_2IF$ and the silicofluorides of certain of these bases. It is shown that the substituted fluorides of sulphur, selenium, and tellurium are much less stable than their other halides. Stability increases from fluorine to iodine, and, in all the halides, with the number of organic radicals in the molecule. There is also an increase in stability in all the series of compounds in passing from sulphur to tellurium. The silicofluorides are more stable than the fluorides.

THE fluorides of sulphur, selenium, and tellurium show decided differences from the other halides of these elements. For instance, in all three cases the maximum covalency of 6 is reached in combination with fluorine, but not with the other halogens, even at low temperatures. The hexafluorides are exceptionally stable, whereas the other halides, including the fluorides, easily hydrolyse and dissociate when heated. Indeed, some doubt exists as to the formation of lower fluorides of selenium and tellurium. Considerable interest, therefore, attaches to the preparation and properties of the alkyl- and aryl-substituted fluorides of these elements. Experiments are described below which seem to show that substituted hexafluorides such as $RSF_5$ are not stable. Certain di- and tri-substituted fluorides have been prepared, and general conclusions are drawn about the stability of these compounds and their relation to the unsubstituted halides. In the table below are given the formulæ of the relevant compounds known previously, and, in italics, those of new compounds now described. The table does not include a number of new silicofluorides which were prepared and characterised.

*Valency* 2.

| X. | $XHal_2$. | $X_2Hal_2$. | XMeHal. | XPhHal. |
|---|---|---|---|---|
| S | $SCl_2$, $SF_2$ | $S_2Cl_2$, $S_2Br_2$ | — | SPhCl, SPhBr |
| Se | — | $Se_2Cl_2$, $Se_2Br_2$ | — | SePhCl, SePhBr |
| Te | $TeCl_2$, $TeBr_2$ | — | — | — |

*Valency* 4.

| X. | $XHal_4$. | $XMeHal_2$. | $XMe_2Hal_2$. | $XMe_3Hal$. | $XPhHal_2$. | $XPh_2Hal_2$. | $XPh_3Hal$. |
|---|---|---|---|---|---|---|---|
| S | $SF_4$, $SCl_4$, $SBr_4$ | — | $SMe_2Cl_2$, $SMe_2Br_2$, $SeMe_2I_2$ | $SMe_3Cl$, $SMe_3Br$, $SeMe_3I$, *$SMe_3F$* | — | $SPh_2Cl_2$, $SPh_2Br_2$, $SPh_2I_2$ | $SPh_3Cl$ |
| Se | $SeCl_4$, $SeBr_4$ | ($SeEtBr_3$) | $SeMe_2Cl_2$, $SeMe_2Br_2$, $SeMe_2I_2$ | $SeMe_3Cl$, $SeMe_3Br$, $SeMe_3I$, *$SeMe_3F$* | $SePhCl_3$, $SePhBr_3$ | $SePh_2Cl_2$, $SePh_2Br_2$ | $SePh_3Cl$, $SePh_3Br$, $SePh_3I$, *$SePh_3F$* |
| Te | $TeCl_4$, $TeBr_4$, $TeI_4$ | $TeMeBr_3$, $TeMeI_3$ *$TeMeF_3$* * | $TeMe_2Cl_2$, $TeMe_2Br_2$, $TeMe_2I_2$ *$TeMe_2F_2$*, | $TeMe_3Cl$, $TeMe_3Br$, $TeMe_3I$, *$TeMe_3F$* | — | $TePh_2Cl_2$, $TePh_2Br_2$, $TePh_2I_2$, *$TePh_2F_2$* | $TePh_3Cl$, $TePh_3Br$, $TePh_3I$, *$TePh_3F$* |

* Not obtained pure.

The resemblance between polyvalent iodine and tellurium has often been discussed. Tervalent iodine forms a series of aryl-substituted halides corresponding in properties to the tellurium compounds; *e.g.*, $PhICl_2$ is non-polar, and $Ph_2ICl$ salt-like. The fluoride $PhIF_2$ was prepared by Dimroth and Bockemüller (*Ber.*, 1931, **64**, 522), but $Ph_2IF$, which was also prepared in the course of this work, has not been described before.

### EXPERIMENTAL.

Since the direct reaction of fluorine with organic substances usually leads to destruction of the organic nucleus, even when the conditions are controlled (Bigelow *et al.*, *J. Amer. Chem. Soc.*, 1933, **55**, 4614; Fredenhagen and Cadenbach, *Ber.*, 1934, **67**, 928), fluorine had to be introduced by indirect procedures, such as the interaction of another halide with a metallic fluoride or anhydrous hydrogen fluoride, or the action of aqueous hydrogen fluoride upon the appropriate oxide

or hydroxide. In all the successful preparations described here, the fluorinating agent was silver fluoride or aqueous hydrogen fluoride.

Silver fluoride was made by dissolving the freshly-precipitated and washed oxide in excess of 40% hydrofluoric acid, and evaporating the solution to dryness on a sand-bath. The product was several times alternately powdered and heated for an hour or so at 200° in a high vacuum. It was stored in a desiccator. Aqueous solutions were filtered before use to remove a little silver and silver oxide. The silver fluoride was employed either in aqueous solution for double decompositions, or anhydrous for preparing non-salt-like fluorides. In the former case the stoicheiometric amount was required, and could be weighed, since the material was almost pure. In the latter case an excess was needed, because of the inefficient contact between the reagents, especially when iodides were being fluorinated and a mixture of silver fluoride and iodide was formed. (This disadvantage in the use of silver fluoride was first noted by Swarts.) The halide to be fluorinated was often dissolved in an inert organic solvent, either because it decomposed below its m. p., or in order to make the reaction less violent.

*Analytical Methods.*—The classical gravimetric method of fluorine determination, precipitation as calcium salt, was abandoned after a few trials because it was tedious, and also not accurate enough where only small quantities of material were available, which was usually the case. An improved form of the volumetric procedure of Willard and Winter (*Ind. Eng. Chem. Anal.*, 1933, **5**, 7; and numerous later articles) was found to be rapid and reliable. The organic compound was dissolved in water, or, if insoluble, hydrolysed with dilute sodium hydroxide solution, giving a solution containing 2—10 mg. of fluorine. The solution was diluted to 30—40 c.c., and 3 drops of 0·05% aqueous sodium alizarinsulphonate solution added. The acidity was adjusted with very dilute hydrochloric acid or sodium hydroxide, so that the indicator was just yellow. 0·5 C.c. of Hoskins–Ferris buffer solution of pH 3·5 (Rowley and Churchill, *ibid.*, 1937, **9**, 551) was added. The sample was titrated with a thorium nitrate solution containing about 6 g. of the commercial salt per l., from a 10-c.c. burette. Good lighting was essential, and it was found that a daylight lamp held close to the flask was satisfactory. The end-point was marked by a permanent pink colour (the thorium–alizarin lake). It was more easily detected by allowing the precipitate of thorium fluoride, which adsorbs the lake, to settle. The thorium nitrate was standardised against pure sodium fluoride. With about 5 mg. of fluorine the estimated titration error was $\pm 0{\cdot}6\%$. In this way samples of the organic substance no larger than 0·05 g. were satisfactorily analysed. The titration succeeds whether the fluorine is present as fluoride or as silicofluoride.

*Fluorination of the Substituted Dihalides.*—No fluorine derivatives in this series were isolated. Attempts were made to replace chlorine by fluorine in PhSCl, *o*-$NO_2{\cdot}C_6H_4{\cdot}SCl$, *o*-$NO_2{\cdot}C_6H_4{\cdot}SBr$, and *p*-$NO_2{\cdot}C_6H_4{\cdot}SCl$, with silver, mercurous, mercuric, and hydrogen fluoride. All these substances reacted with the metallic fluorides, but the product always consisted mostly of the corresponding disulphide, mixed with tarry matter containing some fluorine; hydrogen fluoride was evolved during the reaction. The *p*-$NO_2{\cdot}C_6H_4{\cdot}SCl$ reacted with liquid anhydrous hydrogen fluoride giving a similar mixture of products, but also a small quantity of mixed crystals of *p*-$NO_2{\cdot}C_6H_4{\cdot}SO_2Cl$ and *p*-$NO_2{\cdot}C_6H_4{\cdot}SO_2F$, for the formation of which atmospheric oxidation may have been responsible; the *o*-isomer did not react. PhSeBr reacted vigorously with silver fluoride, but the product was a mixture of high-boiling substances, and no fluorine compound was present which distilled at a lower temperature than the bromide. Antimony trifluoride and ammonium fluoride did not fluorinate PhSeBr.

*Fluorination of the Monosubstituted Tetrahalides.*—$PhSeBr_3$ in benzene solution did not react appreciably with silver fluoride during several hours' heating at 70°, nor did the solid bromide react with liquid anhydrous hydrogen fluoride, with or without antimony pentachloride. An ethereal solution reacted with mercuric fluoride but the product was a crystalline substance containing mercury, probably as a double salt; on the supposition that $PhSeF_3$ might be more salt-like than the other halides, solutions were prepared, which might be expected to contain the fluoride, by double decomposition of the tribromide with silver fluoride in water, and by treating benzeneseleninic acid with excess of 40% hydrofluoric acid, in which it is freely soluble. When allowed to evaporate, these solutions yielded unchanged acid which at first contained a little fluorine, but which lost it on recrystallisation from water.

*Methyltellurium Trifluoride*, $TeMeF_3$.—This compound was not prepared pure but there is evidence that it may exist. The tri-iodide was prepared by Drew's method (*J.*, 1929, 565), and 2·6 g. were added gradually to 10 c.c. of boiling anhydrous acetone containing 6 g. of dry silver fluoride. After 20 minutes, the solution, at first brown, had become colourless. It was filtered and evaporated in a vacuum desiccator. An oil which would not crystallise remained, which had the smell of methyl telluride, and fumed slightly in moist air. A specimen was analysed by hydrolysis and titration (Found: F, 20·7. Calc. for $TeMeF_3$: F, 29·0%). The oil reacted at once with water, precipitating an amorphous white solid (probably the " anhydride " of methanetellurinic acid). After standing for 3 days in a high vacuum, the substance had become converted into a pasty crystalline solid mixed with some liquid, which could not be satisfactorily recrystallised from organic solvents. The initial product was almost certainly impure $TeMeF_3$, which probably disproportionated on standing according to the equation: $2TeMeF_3 \longrightarrow TeF_4 + TeMe_2F_2$. The inaccessibility of $TeMeI_3$ made it impracticable to repeat this preparation.

*Fluorination of the Disubstituted Tetrahalides.*—Because the sulphur compounds in this series, and the methylselenium compounds, are very unstable and decompose at, or slightly above, room temperature, no attempt was made to fluorinate these. Attention was concentrated on the diphenylselenium dihalides and the dimethyl- and diphenyl-tellurium dihalides, in which cases new fluorine compounds were isolated.

Phenyl selenide was first prepared by the methods of Leicester and Bergstrom (*J. Amer. Chem. Soc.*, 1929, **51**, 3587; improved method, *Org. Synth.*, Coll. Vol. 2, 238). In order to prepare $SePh_2Cl_2$, the crude $Ph_2Se$ was dissolved in concentrated nitric acid, concentrated hydrochloric acid added, and the precipitate filtered off, drained, air-dried, and recrystallised from benzene. $Ph_2SeBr_2$ was prepared from the selenide and bromine (Krafft and Vorster, *Ber.*, 1893, **26**, 2818). $SePh_2O,H_2O$ was obtained by boiling the dichloride for a minute with a small excess of 10% sodium hydroxide solution and recrystallised from benzene. $SePh_2Cl_2$ and $SePh_2Br_2$ were rather inert towards fluorides. In unsuccessful attempts to make them react in benzene or toluene solution with silver fluoride, they both reacted preferentially with the solvent and vapours of hydrogen chloride or bromide mixed with hydrogen fluoride and silicon tetrafluoride were evolved. There was no organic product containing more than a trace of fluorine.

*Diphenylselenoxide Hydrofluoride*, $SePh_2O,HF$.—The compound $SePh_2O,H_2O$ was extremely soluble in 40% hydrofluoric acid, as was the seleninic acid. Both compounds behave differently towards the other halogen acids, with which sparingly soluble dihalides are formed. The hydrogen fluoride solutions of the hydrated selenoxide when evaporated on the steam-bath yielded a syrup which crystallised on cooling to a mass of elongated prisms. A quantity of this product was made by pumping off the water and excess acid from such a solution in a waxed vacuum desiccator, and recrystallising it twice from benzene in platinum vessels (Found: F, 6·6, 6·4. $C_{12}H_{10}OSe,HF$ requires F, 7·1%). The *substance* hydrolysed slowly in moist air, forming the hydrated selenoxide. It seems reasonable, therefore, to assign it the formula $SePh_2O,HF$ or $SePh_2F{\cdot}OH$. The m. p. was 75°. The compound was readily soluble in benzene. The solutions instantly attacked glass, forming two new substances, one consisting of large, thin, crystalline plates ($2SePh_2O,H_2SiF_6$), and the other of microscopic, rectangular plates ($3SePh_2O,H_2SiF_6$), both of which were insoluble in benzene.

The former compound was obtained in good yield when a solution of the hydrated selenoxide in excess of 40% hydrofluoric acid was left to evaporate over sulphuric acid in an unwaxed vacuum desiccator, the walls of which presumably supplied the silicon tetrafluoride for the reaction. The product was washed well with benzene to remove $SePh_2O,HF$. It did not melt when heated, but charred gradually above 250°. It was freely soluble in water and the solution gave a gelatinous precipitate with potassium salts, showing that $SiF_6''$ was present (Found: F, 17·7; Se, 23·1. $2C_{12}H_{10}OSe,H_2SiF_6$ requires F, 17·8; Se, 24·5%). The result for selenium (method of Bauer, *Ber.*, 1915, **48**, 507) was low because of adsorption upon gelatinous silica formed by fluoride attack on the walls of the Carius tube. The *substance* lost hydrogen fluoride on standing in moist air, and fell to a microcrystalline powder, consisting of the silicofluoride described next.

The *compound* $3Ph_2SeO,H_2SiF_6$ (above) was prepared in better yield by boiling the hydrated selenoxide with 10% hydrofluosilicic acid for a few minutes, filtering off the insoluble white solid, and recrystallising it twice from boiling ethanol. It consisted then of minute, well-formed, thin, rectangular plates, which were only slightly soluble in cold but appreciably soluble in boiling water. The solution gave the silicofluoride test with potassium sulphate solution. For analysis the substance was dissolved in dilute nitric acid and titrated (Found: F, 12·1, 12·0, 12·4; Se, 25·3. $3C_{12}H_{10}OSe,H_2SiF_6$ requires F, 12·8; Se, 26·5%).

*Dimethyltellurium Difluoride*, $Me_2TeF_2$.—The di-iodide was prepared by Vernon's method (*J.*, 1920, **117**, 90). 3 G. were dissolved in 15 c.c. of anhydrous acetone, and a large excess (6 g.) of silver fluoride was added to the boiling solution. There was a vigorous reaction and the solution became colourless after 20 minutes' boiling and shaking. The silver salts were filtered off, and the filtrate evaporated in a desiccator at the filter-pump. The white flakes of the *difluoride* remaining were recrystallised from 8 c.c. of boiling light petroleum to which 1·5 c.c. of absolute ethanol had been added. The product consisted of sparkling, colourless leaves, which were analysed by dissolving in water and titrating (Found: F, 19·6, 19·8. $C_2H_6F_2Te$ requires F, 19·6%). The difluoride was very soluble in water, ethanol, and acetone, but insoluble in petroleum. It smelt like methyl telluride. Water solutions were acid to methyl-red, so the substance was probably strongly hydrolysed. It was, however, perfectly stable in moist air. The m. p. was 84° and decomposition began at 208° with formation of a black residue (probably tellurium).

*Diphenyltellurium Difluoride*.—The phenyl telluride required was present in the ethereal solution from the preparation of triphenyltellurium iodide (see below), which was dried over calcium chloride and evaporated to a small bulk. An ethereal solution of 3 g. of iodine was added gradually until the di-iodide had precipitated completely and the solution was yellow. The precipitate was filtered off and washed with ether. The di-iodide was added in small portions to a refluxing mixture of 15 c.c. of dry toluene and 2 g. of dry silver fluoride. Each addition was made when the red colour due to the last had disappeared. The hot solution was filtered at the pump, and immediately deposited small colourless crystals of the *difluoride*, which were filtered off, washed with toluene, and recrystallised from benzene. For analysis, the substance was hydrolysed by boiling with 2N-sodium hydroxide for a short time. [The telluroxide first formed redissolved after a little boiling, perhaps as $TePh_2(OH)_2$.] (Found: F, 12·1, 11·8. $C_{12}H_{10}F_2Te$ requires F, 11·9%). The difluoride formed small rhombs, moderately soluble in benzene and toluene and very soluble in chloroform. It was unaffected by the atmosphere and insoluble in water. It melted at 154° and began to decompose at 290°. This compound could be prepared similarly from the dibromide and silver fluoride in boiling benzene, but the reaction is slower.

*The Trisubstituted Tetrahalides*.—The compounds in this series were salt-like. Nearly all the fluorides can be prepared. The chief experimental difficulties arose from their very great solubility in water, accompanied usually by extreme deliquescence and a tendency to separate from organic solvents in a liquid form. The silicofluorides, which were well-crystallised and stable, were prepared and examined in cases where the fluorides were difficult to purify. In all cases the fluorine analyses were performed by dissolving the salts in water and titrating them with thorium nitrate.

*Trimethylsulphonium Fluoride*.—The iodide was prepared by mixing 6 g. of methyl sulphide and 14 g. of methyl iodide. After standing for 24 hours, the solid cake which had formed was recrystallised once from ethanol, giving an almost theoretical yield of the sulphonium iodide, from which a trace of iodine was removed by ether washing. 4·3 G. of silver fluoride were dissolved in 10 c.c. of water, the solution filtered, and to it was gradually added the equivalent quantity of the sulphonium iodide (7 g.), dissolved in a little water, until precipitation of silver iodide was just complete. The latter was filtered off in the cold, and the filtrate evaporated in a platinum dish in a vacuum desiccator. Crystallisation began after 2 days and was complete after 4 days over phosphoric oxide in a second vacuum desiccator. A dry specimen was analysed (Found: F, 17·0, 16·7. $C_3H_9SF,H_2O$ requires F, 16·8. $C_3H_9SF$ requires F, 19·8%). The fact that the *substance* decomposed at 123° without melting showed that the water was present as crystal water and not as free water. The fluoride was extremely soluble in water and liquefied in moist air as quickly as phosphoric oxide. It was very soluble in ethanol and insoluble in anhydrous acetone or ether. It separated as a liquid from acetone–ethanol mixtures in attempts at recrystallisation.

*Trimethylsulphonium Silicofluoride*.—A standard solution of the silver salt was made by digesting a weighed excess of silver oxide with 10% hydrofluosilicic acid and filtering off, washing, drying, and weighing the excess oxide. The equivalent quantity of trimethylsulphonium iodide, dissolved in a little water, was added to a measured volume of the silver solution, and the mixture was boiled, filtered, and evaporated to dryness on the steam-bath. The residue was recrystallised once from 95% ethanol. The *silicofluoride* formed colourless needles which did not deliquesce. It was very soluble in water, sparingly soluble in ethanol and insoluble in acetone or ether. It decomposed at 323° without melting (Found: F, 39·3. $C_6H_{18}S_2F_6Si$ requires F, 38·6%).

*Triethylsulphonium Fluoride*.—This compound was less stable than the methyl analogue and was not prepared pure. A solution of the iodide was subjected to double decomposition with silver fluoride in the same way as for the methyl compound. During the evaporation, after crystallisation had begun, ethyl sulphide vapour was evolved. The product consisted of sticky crystals which could not be dried (Found: F, 22·1, 21·8. Calc. for $C_6H_{15}SF$: F, 13·8%. Calc. for $C_6H_{15}SF,HF$: F, 24·0%). An aqueous solution of the crystals was acid to methyl-red. The normal fluoride may decompose thus: $Et_3S^+ \longrightarrow Et_2S + Et^+$; $Et^+ + OH^- \longrightarrow EtOH$; $Et_3SF + H^+ + F^- \longrightarrow Et_3SF,HF$. $SePh_2F$ was found to decompose similarly (see below).

*Triethylsulphonium silicofluoride* was prepared like the methyl compound but with evaporation in a vacuum instead of on the steam-bath, because solutions of this silicofluoride are unstable at 100°. The product was recrystallised by adding dry ether to its solution in acetone–ethanol (10 : 1). It separated in small colourless needles (Found: F, 29·9. $C_{12}H_{30}S_2F_6Si$ requires F, 30·0%). The salt was very soluble in water and ethanol, insoluble in acetone and ether, and, unlike other silicofluorides, very deliquescent. It decomposed at 208° without melting.

*Trimethylselenonium Fluoride*.—$Me_2SeI,I_2$ was made from black selenium and methyl iodide (Scott, *Proc.*, 1904, **20**, 156). It was dissolved in a little ethyl acetate and precipitated with ether, filtered off, washed with ether, and redissolved in ethyl acetate. Water was added, and hydrogen sulphide passed in until the solution was colourless. The mixture was filtered and the iodide precipitated by adding much acetone.

The iodide was only slightly soluble in water. The fluoride and silicofluoride were therefore made from the free base. 7 G. of trimethylselenonium iodide were ground with silver oxide and water, and the solution filtered. It was neutralised to phenolphthalein with very dilute hydrofluoric acid in a platinum dish. The solution was evaporated in a vacuum over sulphuric acid and then over phosphoric oxide for several days. The crystals were dissolved by adding the minimum

of absolute ethanol to their suspension in boiling anhydrous acetone. The salt did not crystallise on cooling, but separated as colourless needles when ether was added to the cold solution. If ether was added to an ethanol solution it separated as a liquid. Analysis showed that the product was a *monohydrate* (Found, in two preparations: F, 11·9, 11·8. $C_3H_9SeF,H_2O$ requires F, 11·8%). The substance was very deliquescent and very soluble in water or ethanol but only slightly soluble in acetone and ether. It decomposed without melting at 124°.

*Trimethylselenonium Silicofluoride.*—A solution of the hydroxide, prepared as described above, was neutralised to methyl-red with hydrofluosilicic acid. The residue after evaporation on the steam-bath was recrystallised from 80% ethanol. The *salt* then consisted of well-formed rhombs, very sparingly soluble in absolute ethanol, but freely soluble in water and not deliquescent. It decomposes at 300° without melting (Found: F, 29·5. $C_6H_{18}Se_2F_6Si$ requires F, 29·4%).

*Triphenylselenonium Fluoride.*—$SePh_3Cl,2H_2O$ was prepared by the method of Leicester and Bergstrom (*loc. cit.*). The *fluoride* was obtained by double decomposition in aqueous solution with the equivalent of silver fluoride. Upon evaporation in a vacuum large anhydrous octahedra slowly crystallised out (Found: F, 5·65, 5·6, 5·6. $C_{18}H_{15}SeF$ requires F, 5·8%). The fluoride was very deliquescent, very soluble in water, ethanol, and chloroform, and moderately soluble in anhydrous acetone. It decomposed at 145° without melting.

No satisfactory method of recrystallisation was found. When solutions of this fluoride were evaporated on the steam-bath, it did not crystallise out. Instead, the syrupy residue separated into a lower viscous layer and an upper mobile layer. The latter was identified as phenyl selenide by conversion into the chloride, m. p. 179°. The lower layer solidified to a mass of brown needles when heating was continued; these consisted of the acid fluoride $SePh_3F,HF$ (below). The hydrolysis reaction recalls that of $SEt_3F$.

*Triphenylselenium Hydrogen Fluoride,* $Ph_3SeF,HF$.—A solution of the normal fluoride was filtered into a platinum dish and treated with one equiv. of 40% hydrofluoric acid, which was weighed out in a platinum crucible. The solution crystallised easily when evaporated in a vacuum. The *substance* recrystallised from anhydrous acetone in colourless needles, m. p. 99° (Found: F, 10·3. $C_{18}H_{16}SeF,HF$ requires F, 10·9%); a specimen made by decomposition of an aqueous normal salt solution (Found: F, 10·5; Se, 21·6. Calc.: F, 10·9; Se, 22·6%) had m. p. 100°; mixed m. p. 98—99°.

*Triphenylselenonium Dihydrogen Fluoride,* $SePh_3F,2HF$.—This *compound* resulted when an excess of 40% hydrofluoric acid was added to a solution of the normal fluoride and the solution was evaporated in platinum upon the steam-bath. The product was recrystallised from dry acetone in platinum vessels; colourless needles, m. p. 117—120°, were obtained (Found: F, 15·2. $C_{18}H_{15}SeF,2HF$ requires F, 15·5%). The compound was more soluble in acetone than the mono-acid salt; the solution attacked glass rapidly, forming a shower of minute crystals of the silicofluoride.

*Triphenylselenonium Silicofluoride.*—A solution of the chloride dihydrate was decomposed with silver silicofluoride, and the filtered product evaporated on the steam-bath. The residue, recrystallised from acetone containing a little water, separated in small hexagonal tablets (decomp. 228°), very soluble in water and ethanol, but insoluble in acetone and ether (Found: F, 15·6. $C_{36}H_{30}Se_2F_6Si$ requires F, 15·0%). A small quantity of this *compound* was found in the products of the hydrolytic decomposition of the fluoride.

*Trimethyltelluronium Fluoride.*—$TeMe_3I$ and $TeMeI_3$ were prepared by Drew's method (*J.*, 1929, 565). The former was recrystallised once from water; 2·5 g. were converted into the base by grinding in a mortar with excess of silver oxide and a little water. One half of the filtered base solution was neutralised to phenolphthalein with dilute hydrofluoric acid in a platinum dish and evaporated in a vacuum over sulphuric acid. The white cake remaining after 24 hours was recrystallised from anhydrous acetone containing the minimum of absolute ethanol to dissolve the salt. The fluoride separated in thin leaves. The crystals obtained from moist specimens were long needles, stable in ordinary air, efflorescent in a desiccator, and deliquescent in moist air. The anhydrous *salt* (Found: F, 9·5. $C_3H_9TeF$ requires F, 9·65%) was deliquescent. By analogy with the corresponding sulphur and selenium compounds, the hydrate is probably a monohydrate. The fluoride was very soluble in water and ethanol and insoluble in acetone and ether. It decomposed at its m. p., 128°, disappearing completely and producing an odour of methyl telluride.

*Trimethyltelluronium Silicofluoride.*—The other half of the hydroxide solution (above) was neutralised to methyl-red with hydrofluosilicic acid and evaporated to dryness on the steam-bath. The residue was recrystallised from 80% ethanol, from which the *silicofluoride* separated in large thin rhombs (Found: F, 23·7. $C_6H_{18}Te_2F_6Si$ requires F, 23·5%), insoluble in acetone and ether, slightly soluble in alcohol and freely soluble in water. The crystals did not deliquesce; they decrepitated at 210° and decomposed at 320—336°.

*Triphenyltelluronium Fluoride.*—Tellurium tetrachloride (Michaelis, *Ber.*, 1887, **20**, 1780) was converted by reaction with phenylmagnesium bromide into the telluronium bromide (Lederer, *Ber.*, 1911, **44**, 2289), which was obtained in better yield than by Lederer by recrystallising it from ethanol instead of converting it into the iodide. The bromide was converted into the base by treatment with silver oxide in cold water. (If the mixture was boiled, as Lederer describes, the base instantly decomposed.) The base solution was neutralised with hydrofluoric acid and evaporated in a vacuum. The *fluoride* was recrystallised from dry acetone, in which it was moderately soluble (Found: F, 5·2. $C_{18}H_{15}TeF$ requires F, 5·05%). This was the most stable fluoride of the series. It did not deliquesce or separate as a liquid from solutions. The crystals were stumpy prisms, very soluble in water and ethanol, but insoluble in ether. Decomposition began near 190° and at 203° the compound melted and decomposed suddenly.

*Diphenyliodonium Fluoride,* $Ph_2IF$.—15 G. of phenyliodonium chloride were ground with a small excess of 5% sodium hydroxide solution and the paste shaken for 24 hours in a stoppered bottle. The yield of iodosobenzene after collection and washing was only 5 g. Some of the material had become converted into soluble salts and 3·5 g. of diphenyliodonium iodide were precipitated from the filtrate by adding excess of potassium iodide solution.

6·5 G. of iodoxybenzene were prepared from 10 g. of iodobenzene by Ortoleva's method (*Chem. Zentr.*, 1900, I, 723). The iodoso- and iodoxy-benzene were used to prepare diphenyliodonium iodide (Hartmann and Meyer, *Ber.*, 1894, **27**, 502); yield 3·5 g.

The two yields of this iodide were shaken with an excess of silver oxide and 30 c.c. of water for 6 hours. The resulting solution of iodonium hydroxide was filtered off and divided into two parts. One portion of the base solution was neutralised to phenolphthalein with dilute hydrofluoric acid, and the solution evaporated to small bulk on the steam-bath. The evaporation was completed over sulphuric acid and then over phosphoric oxide in a vacuum. The *fluoride* was recrystallised twice from dry acetone, separating in large colourless rhombs, which deliquesced in moist air (Found: F, 6·3, 6·3. $C_{12}H_{10}FI$ requires F, 6·35%). It was very soluble in water and in ethanol and insoluble in ether; it melted with decomposition at 85° and decomposed quickly at 110°, and it was photosensitive, becoming dark brown after a few days in daylight.

*Diphenyliodonium Silicofluoride.*—The second portion of the base solution (above) was neutralised to methyl-red with hydrofluosilicic acid and evaporated to dryness on the steam-bath. The residue was recrystallised twice from absolute ethanol. The *silicofluoride* formed small pointed prisms which were not deliquescent (Found: F, 16·5. $C_{24}H_{20}I_2F_6Si$ requires F, 16·2%), but were easily soluble in water, sparingly soluble in ethanol, and insoluble in acetone and ether; m. p. 187° (decomp.). The salt was stable to light.

*Higher-substituted Fluorides.*—No analogues of the compounds $SRF_3$, $SRF_5$ and $SeRF_5$ exist for the other halogens. It was therefore necessary to choose methods of preparation other than by way of the usual metal fluorides or hydrogen fluoride. Experiments were made on the following lines: (1) The action of Grignard reagents upon sulphur tetra- and hexa-fluoride. (2) The action of fluorine, or phenyliodonium fluoride, upon the organic disulphides and diselenides

(1) Gaseous sulphur hexafluoride bubbled through an ethereal solution of phenylmagnesium bromide did not react below the b. p. of ether. Liquid "sulphur tetrafluoride," prepared in an impure state from cobaltic fluoride and sulphur (Fischer and Jaenckner, *Z. angew. Chem.*, 1929, **42**, 810), reacted violently with phenylmagnesium bromide in ether at −60°. The products, however, contained no volatile fluorine compound and apparently consisted of PhSBr and bromine, which were not, however, positively identified. Phenylmagnesium iodide reacted to give iodine as the only volatile product. The following mechanism may be suggested:

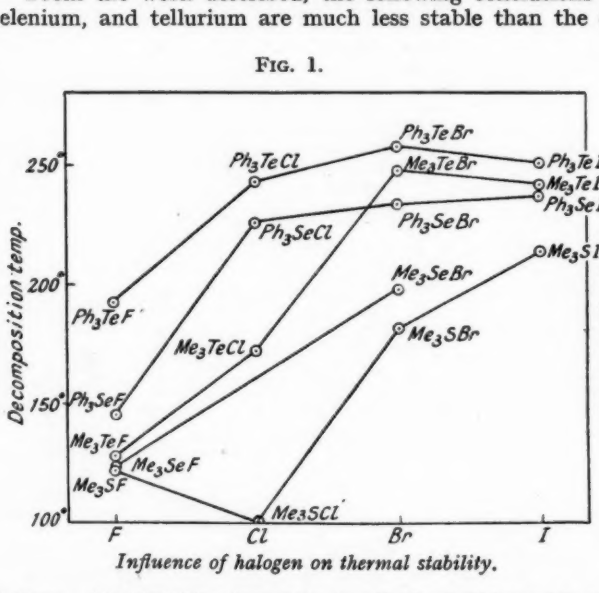
$$PhMgBr(I) + SF_4 \longrightarrow PhSF_3 + MgBr_2(I_2) + MgF_2$$
$$PhSF_3 + MgBr_2(I_2) \longrightarrow PhSBr_3(I_2) + MgF_2$$
$$PhSBr_3 \longrightarrow PhSBr + Br_2$$
$$PhSI_3 \longrightarrow Ph_2S_2 + I_2 \text{ (PhSI does not exist)}$$

(2) The reaction at 0° between fluorine–nitrogen mixtures and chloroform solutions of diphenyl diselenide or *o*- or *p*-nitrophenyl disulphide yielded only hydrogen fluoride and tarry or high-boiling condensation products. Phenyliodonium fluoride, prepared by Dimroth and Bockemüller's method (*Ber.*, 1931, **64**, 522), reacted similarly, although it was established by separate experiments that the analogous reactions of the iodonium chloride with phenyl selenide gave excellent yields of phenylselenonium dichloride.

## Discussion.

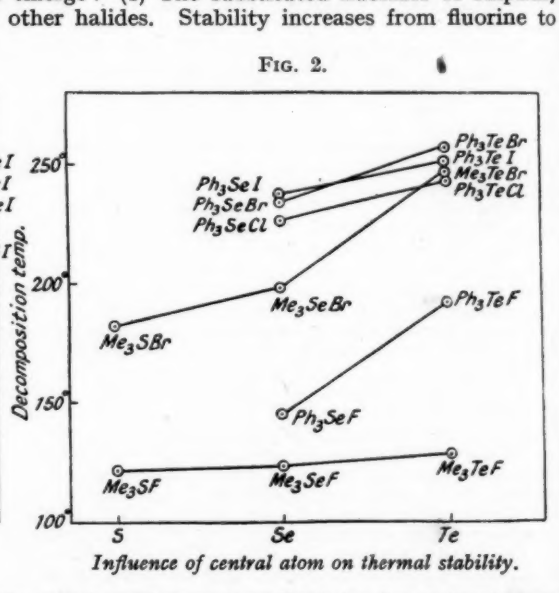
From the work described, the following conclusions emerge: (1) The substituted fluorides of sulphur, selenium, and tellurium are much less stable than the other halides. Stability increases from fluorine to iodine. (2) Stability increases in all the halides with the number of organic radicals in the molecule, and most noticeably in the fluorides. (3) Stability increases from sulphur to tellurium.

Fig. 1.




*Influence of halogen on thermal stability.*

Fig. 2.




*Influence of central atom on thermal stability.*

Therefore, in those cases where the chlorine derivatives are on the verge of decomposition at room temperature, it seems unlikely that fluorine derivatives could be prepared. It was only with tellurium that more than one atom of another halogen was replaced by fluorine, and stable compounds ($TeMe_2F_2$ and $TePh_2F_2$) obtained. In experiments designed to prepare corresponding compounds of sulphur and selenium, hydrogen fluoride was evolved and the organic residues were complex, pointing to condensation reactions between the ·SF and ·SeF grouping and the organic nucleus. The chlorides and bromides decompose similarly but less easily.

The salt-like substituted halides of sulphur, selenium, tellurium and iodine always decompose in the same way, *e.g.*, $SMe_3I \longrightarrow SMe_2 + MeI$; $Ph_2ICl \longrightarrow PhI + PhCl$, forming on the one hand an aryl iodide or a dialkyl or diaryl sulphide, selenide, or telluride, and on the other hand an alkyl or aryl halide. $Et_3OBF_4$ decomposes similarly, behaving as a compound of $Et_3OF$ and $BF_3$: $Et_3OBF_4 \longrightarrow Et_2O,BF_3 + EtF$ (Meerwein *et al.*, *J. pr. Chem.*, 1937, **147**, 257).

The decomposition could take place by either of two mechanisms. The cation may disrupt, giving a free organic radical with unit positive charge, which afterwards combines with the anion; or an intermediate covalent form of the substance in which the central atom has a decet valency group may be formed. Fajans's principle excludes the latter hypothesis, for such a covalent form would result most easily in the case of the most easily deformed anion, that is, in the iodides, and least easily in the fluorides. Actually (see Fig. 1) the iodides are the most stable thermally, and the fluorides the least stable. On the other hypothesis, the crucial factors deciding decomposition are the intrinsic strength or weakness of the cation structure and the degree of

deformation it suffers from the neighbouring anions. The fluoride ion produces the greatest deformation, and the cations containing sulphur, with its relatively small tendency to assume a positive charge, break up more easily than those containing the more metallic tellurium, because in the former the ionic charge will be located less centrally and more peripherally than in the latter. The observations are shown in Fig. 2, which illustrates the influence of the central atom on the thermal stability, and are in accordance with this idea. The decomposition temperatures in these diagrams are not individually well defined, but they show very definite trends. The decomposition of a typical compound $XR_3Hal$ probably takes place thus: $(R_3X)^+Hal^- \longrightarrow R_2X + X^+ + Hal^-$; $X^+ + Hal^- \longrightarrow XHal$. Lucas, in studying the decomposition of *o*-tolyliodonium iodide, came to the same conclusion through a different argument (*J. Amer. Chem. Soc.*, 1936, **58**, 157).

The greatest changes in thermal stability should be produced by correspondingly great changes in ionic radius, *i.e.*, in passing from fluorine to chlorine and from oxygen to sulphur. In fact, the fluorides are much less stable than the chlorides and the oxonium salts are so much less stable than the sulphonium salts that $Et_3OI$, in theory the most stable oxonium halide, cannot be prepared (Meerwein, *loc. cit.*). The silicofluorides, in which the small free $F^-$ ion is replaced by the large $SiF_6^{--}$ ion with its relatively small distorting power, are highly stable.

With sulphur and selenium, octet valency groups are usual in combination with the heavier halogens and in combination with fluorine the duodecet is the only stable grouping. The lower sulphur fluorides disproportionate very easily so as to restore the duodecet. Tellurium alone forms stable tetrahalides with a decet valency group, although sulphur and selenium show a weak tendency towards the decet. The results of the attempts to fluorinate the phenyl sulphur halides can be explained as follows: The phenyl sulphur fluoride first formed disproportionated to a mixture of the disulphide and a higher fluoride [*e.g.*, $p$-$NO_2{\cdot}C_6H_4{\cdot}SF$ to $(p\text{-}NO_2{\cdot}C_6H_4{\cdot}S)_2$ and $p$-$NO_2{\cdot}C_6H_4{\cdot}SF_3$ or $p$-$NO_2{\cdot}C_6H_4{\cdot}SF_5$]; the latter then decomposed by intermolecular condensations to hydrogen fluoride and tarry products. Similarly for selenium. With tellurium, however, the stability of the decet facilitated the formation of diphenyl- and dimethyl-tellurium difluorides.

According to Pauling, even the bonds between non-metals and fluorine can be strongly ionic. When $SePh_2O$ and $Ph{\cdot}SeO_2H$ are treated with aqueous hydrochloric, hydrobromic, or hydriodic acid, insoluble covalent compounds are formed but these two bases are freely soluble in aqueous hydrofluoric acid, probably because the fluorine remains ionised instead of assuming a predominantly covalent binding like the other halogens. Upon evaporation the ions $Ph_2Se^{++}$ and $PhSe^{+++}$ separate as $Ph{\cdot}SeO_2H$ or $SePh_2O,HF$, because the small solubility products of the bases are exceeded first. The weakness of hydrofluoric acid, making for a higher concentration of hydroxyl ions, is a contributory factor.

Previous experiments on the fluorination of sulphur halides by Ruff (*Ber.*, 1906, **39**, 4310) with antimony pentafluoride, Moissan (*Bull. Soc. chim.*, 1891, **5**, 456) with silver fluoride, and Guntz (*Compt. rend.*, 1884, **98**, 819) with lead fluoride, and of selenium tetrachloride by Prideaux and Cox (*J.*, 1928, 1603) all gave indefinite results. According to work described above, it seems that the substituted halides are generally rather resistant to conversion into fluorides, only vigorous reagents, such as silver fluoride, being effective. The halides of bivalent sulphur and selenium are the most reactive; the mono- and di-substituted tetrahalides of quadrivalent tellurium are moderately reactive, and $SePhBr_3$ could not be fluorinated by silver fluoride. Together with Thiel's observation that sulphur tetrachloride is not converted into fluoride by silver fluoride or antimony trifluoride (Thesis, Berlin, 1905), these facts support the theory that fluorinations take place through co-ordination of fluoride ions with the central atom of the halide. Sulphur tetrachloride and $PhSeBr_3$ lose some of their halogen very easily and could not therefore be expected to attach further radicals by co-ordination. $SHal_6^{--}$ ions do not exist, $SeHal_6^{--}$ ions are unstable, and $TeHal_6^{--}$ ions fairly stable, showing the relative ease of co-ordination of halogen ions.

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## 251. *The Chemistry of the Higher Silanes. Part I. Tetrasilane.*

By H. J. EMELÉUS and A. G. MADDOCK.

Some physical constants of tetrasilane have been redetermined and some new observations made on its chemical properties, especially with respect to its thermal stability and iodination.

IN 1902 Moissan and Smiles began the study of the chemistry of the higher silanes with the isolation of a crude specimen of mixed higher hydrides from the product of the action of hydrochloric acid on magnesium silicide. The formula $Si_2H_6$ was attributed to this material (*Ann. Chim. Phys.*, **27**, 5). Later they prepared a relatively pure specimen of $Si_2H_6$ from lithium silicide (*Compt. rend.*, 1902, **134**, 1083). In 1909 Lebeau prepared mono- and di-silane and noted the presence of higher hydrides of lower volatility but believed these to be unsaturated compounds (*ibid.*, **148**, 43). The preparation of the silanes from magnesium silicide and acids was investigated in great detail in 1912 by Besson who much improved the yield of previous workers (*ibid.*, **154**, 116, 1603). Stock, in the period 1916—1923, improved but little on the preparative details of

Besson but isolated tri- and tetra-silane from the products. The former he characterised by the determination of a number of its chemical and physical properties. The latter he obtained only in small quantity, all his observations being conducted on 1 c.c. of crude material, but he determined the melting point and a few points on the vapour-pressure curve. The extrapolated boiling point was given approximately. Stock reported both these compounds to be unstable at room temperature. Trisilane was said to show signs of decomposition after 12 months' storage in glass bulbs at room temperature, and tetrasilane was found to have changed its vapour pressure appreciably after 3 months. A yellow polymeric solid silicon hydride was reported to be formed in these reactions. The only other reactions observed with these hydrides were their oxidation by air and oxygen, their complete hydrolysis by alkalis, their reduction by sodium amalgam, and their reaction with chloroform in the presence of anhydrous aluminium chloride. In 1935 Johnson and Isenberg (*J. Amer. Chem. Soc.*, **57**, 1349) prepared silanes by the action of ammonium bromide on magnesium silicide in liquid ammonia, obtaining a 65—80% conversion of silicon into hydrides and thereby much improving on Stock's yield of about 25% conversion. The influence of the mode of preparation of the magnesium silicide on the yield was stressed by these authors.

## Experimental.

The yield of silicon converted into hydride by the acid decomposition of magnesium silicide is so dependent on the conditions of the reaction that some details of the preparation are given. The magnesium silicide ($Mg_2Si$) was prepared by heating crushed silicon of 99·0% purity (sieved 90 mesh) with a 10% excess of magnesium turnings, prepared from a 99·9% magnesium ingot. The mixture, contained in a soft-iron boat, was heated in a stream of pure hydrogen in a steel tube in a furnace. The effects of temperature and duration of heating were investigated. The yield of hydrides increased with up to 24 hours' heating of the magnesium–silicon mixture, but further heating up to 48 hours produced no very pronounced change (these observations were made on silicide prepared at 600° and 700°). The yields of hydrides from preparations carried out at 400° and thence at intervals of 50° up to 800° were determined under the same conditions of decomposition. Each of these preparations was heated for 24 hours at the temperature stated. In the preparations at 400° and 450° the reaction was obviously incomplete and a test-tube experiment showed the yield of hydrides to be very small; these samples were not tested further. Samples of material prepared at the other temperatures were decomposed by acid, as described later, and the percentage of the silicon converted into hydride was determined. The following results were obtained.

| Temp. of prepn. | 500° | 550° | 600° | 650° | 700° | 750° | 800° |
|---|---|---|---|---|---|---|---|
| Yield (% of Si converted) | 16 | 22 | 27 | 38 | 30 | 25 | 17 |

The yields in the above table are based on measurements of the quantities of the hydrides isolated by the vacuum-fractionation procedure described below.

The relative proportions of the hydrides present in the crude product also changed with the temperature of the preparation. The product obtained at the higher temperatures was darker and gave a relatively increased yield of the higher silanes. The best over-all yield was obtained from the silicide prepared at 650°. These observations are in accordance with those of Johnson and Isenberg and support the view that the higher silanes result from the decomposition of a magnesium silicide other than $Mg_2Si$ which is stable in the Mg–Si system at temperatures above 600°. Gire's results (*Compt. rend.*, 1933, **196**, 1404) suggest that this silicide may be MgSi. The magnesium silicide prepared in this manner was a purple-blue, crystalline powder. It possessed a musty smell, possibly due to the traces of silicon hydrides formed by atmospheric hydrolysis. When exposed to the atmosphere the silicide deteriorated, and it should therefore be stored in an air-tight container. The yield of hydride from an average specimen fell from 35% to 18% after two months' exposure to a moist atmosphere.

The decomposition of the silicide was carried out in a 3 l. Pyrex flask with walls of double thickness, fitted with inlet and exit tubes and a hopper enabling the silicide to be added in small portions. The inlet tube was connected to supplies of pure hydrogen and nitrogen. The exit tube led through a pair of wash-bottles and a calcium chloride and phosphoric oxide drying train to a pair of condensation traps connected to the vacuum apparatus and a mercury bubbler exit tube. The reaction was carried out in a stream of hydrogen; at the completion of the reaction the hydrogen was replaced by nitrogen to reduce the possibility of explosion on cleaning out the reaction flask. The highest yield was obtained with a 15% hydrochloric acid solution (15% HCl by weight). In each run 2 l. of this acid and 75 g. of silicide were used. Further, the highest yield was obtained when the decomposition was carried out as quickly as possible. It was found inadvisable, however, to allow the temperature of the reaction to rise above 65°, for it then become uncontrollable. Under these conditions a conversion of about 35% of the silicon contained in the silicide into silicon hydrides was consistently obtained.

The fractionation of the crude hydrides was carried out in a Stock-type universal vacuum apparatus. The final purification of materials for determination of physical constants, and a number of the reactions were carried out in all-glass vacuum systems with sealing capillaries, and making use of the magnetic breaker technique. Soda glass (G.E.C. X7) was used entirely in the construction of the apparatus. It was pretreated before use by washing in concentrated nitric acid followed by distilled water. The laboratory in which this research was carried out was illuminated only by diffuse daylight or ordinary electric light.

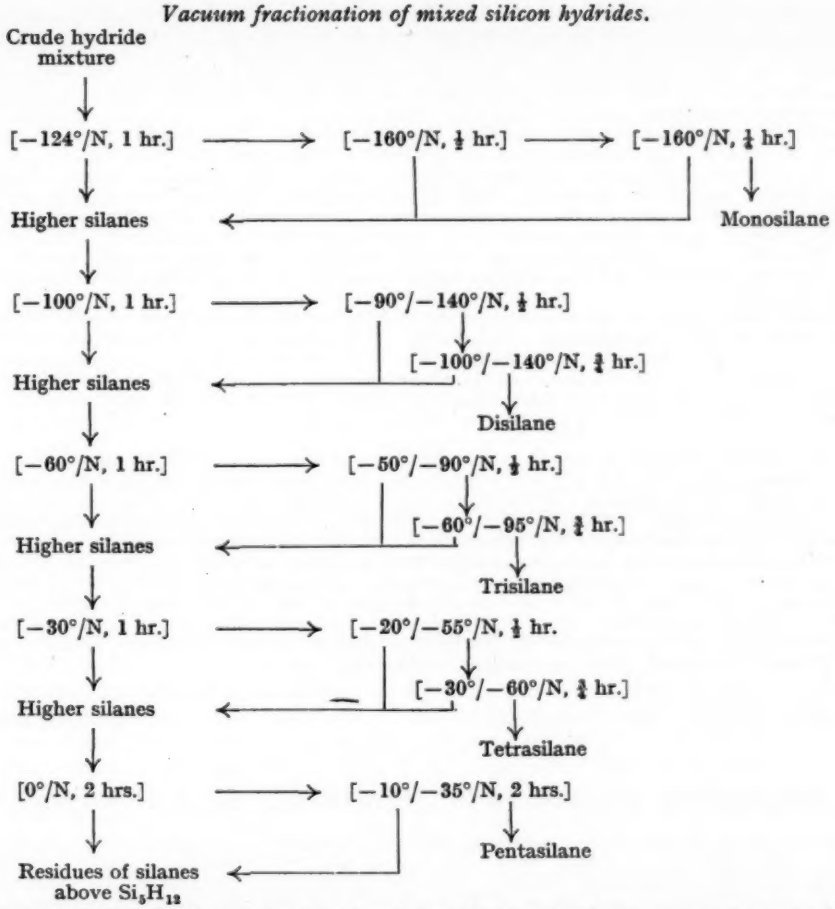
The initial fractionation of the hydrides was performed according to the scheme outlined below.

Specimens of mono-, di-, and tri-silane were fractionated to constant vapour pressure, and their physical properties found to be in complete agreement with the values given by Stock. Samples of these hydrides stored over mercury showed no signs of decomposition after 2 years' storage (average room temp. = 15°). In no case was an appreciable change in vapour pressure produced.

A sample of 8 c.c. of tetrasilane was isolated from a series of fractionations as described above and further purified by a series of 8 fractional distillations and condensations. The product was tensimetrically homogeneous; 4 c.c. of this material were prepared. The crude tetrasilane decomposed slowly on storage at room temperature. The vapour pressure at 12° of a sample of 2 c.c. of the crude material showed the following change (in mm.):

| Initial value | 3 months | 6 months | 9 months |
|---|---|---|---|
| 17 | 22 | 26 | 35 |

*Vacuum fractionation of mixed silicon hydrides.*




[In the above chart the left-hand temperature of each bracketed group is the temperature at which the material was distilled in vacuum. The other temperatures are those of the baths in which the various fractions were condensed from the vapour stream. N denotes a trap cooled in liquid nitrogen. The times for which the various distillations were run are inserted in each case. All fractions collected at liquid nitrogen temperature (after removal of $SiH_4$) were united and stored separately. To illustrate the procedure, the separation of monosilane was done by taking that part of the mixture which distilled in a vacuum at −124° but condensed in liquid nitrogen, and redistilling this at −160° for ½ hr. The residue at −160° was added to the material not volatile at −124°. The volatile material was redistilled at −160° for ½ hr., and the material condensed in the trap at liquid nitrogen temperature was found to be pure monosilane. The residue at −160° was added to the higher silane residue, as shown.]

The purified tetrasilane maintained a vapour pressure of 20·2 mm. at 12° for 12 months. Other observations on samples of intermediate purity support the view that the decomposition is autocatalytic and also strongly catalysed by traces of higher hydrides. The products of this low-temperature catalysed decomposition have not been completely identified. Some hydrogen is produced and traces of liquid silicon hydrides of very low volatility. These must be either much higher members of the silane series or unsaturated silicon hydrides. The latter hypothesis seems unlikely in view of our knowledge of silicon chemistry. At no stage during this research was any compound corresponding to Stock's polymeric yellow hydride obtained. Even in the residues from the decomposition of higher hydrides all the products of decomposition were liquid.

Analysis of the tetrasilane was effected by pyrolysis in a silica tube, giving the silicon content of the compound; and by complete hydrolysis by sodium hydroxide, which determined the number of Si–Si and Si–H bonds (Found: Si, 91·8, 92·0, 91·8. Calc. for $Si_4H_{10}$: Si, 91·7%). The hydrolysis experiments gave

$$\frac{\text{Vol. of } H_2 \text{ obtained (N.T.P.)}}{\text{Vol. of } Si_4H_{10} \text{ (as gas at N.T.P.)}} = 12{\cdot}98,\ 12{\cdot}97,\ 12{\cdot}98 \text{ (Calc. for } Si_4H_{10}\text{: } 13{\cdot}0).$$

The m. p. was determined with a carbon dioxide vapour-pressure thermometer. Two samples were examined, and each had a sharp m. p.: − 84·5°, − 84·2°, − 84·3°, − 84·2° (mean − 84·3°).

The vapour-pressure curve was determined on a pure sample of tetrasilane sealed in a glass spoon-gauge tensimeter. The tensimeter gave a deflection of about 3 mm./mm. Hg pressure difference, and hence by reading with a magnifying glass the pressure could easily be measured, correct to 0·1 mm. Hg. A calibrated thermometer graduated in 0·2° and read to a tenth of a degree was used. The tensimeter was immersed in a thermostatically controlled oil-bath. The mercury column used to record the pressure was at 20° during the experiment. The following values were obtained:

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Temp. ..... | 0·0° | 5·2° | 11·0° | 15·3° | 19·2° | 21·8° | 24·8° | 32·5° | 36·2° | 42·1° | 47·2° | 53·9° |
| Press. (mm. Hg at 20°) | 9·1 | 11·8 | 16·1 | 20·6 | 24·7 | 28·7 | 33·2 | 48·5 | 56·9 | 75·1 | 94·1 | 123·4 |
| Temp. ..... | 56·0° | 61·0° | 64·3° | 69·2° | 73·1° | 77·8° | 81·7° | 84·9° | 88·7° | 91·1° | 94·3° | 96·2° |
| Press. (mm. Hg at 20°) | 133·9 | 161·9 | 182·5 | 221·2 | 254·1 | 297·2 | 339·2 | 377·0 | 426·4 | 458·9 | 504·8 | 535·4 |

Extrapolation gave the b. p. of $Si_4H_{10}$ as 107·4°. The latent heat at the b. p. was 8500 cals./mol. and Trouton's constant was 22·2. The determination of the vapour-pressure curve occupied 7 hours, for 3 hours of which the tetrasilane was at above 70°. At the end of the experiment the vapour pressure of the specimen at 22° had increased by 1 mm. The liquid was still crystal clear, and the material could still be condensed completely by liquid nitrogen, showing that no hydrogen had been formed. In view of the unexpected thermal stability of the tetrasilane further investigation was deemed desirable.

A second sample of pure tetrasilane was sealed in a glass tensimeter. The quantity was arranged to be such that at about 300 mm. Hg pressure the compound had all volatilised. The system was then steadily heated in an oil-bath, and readings of the pressure, temperature, and time from the commencement of heating noted. The state of the tetrasilane vapour could also be visually examined. 0·03 G. of tetrasilane was taken and rapidly heated to 107°; subsequently the temperature was raised gradually to 284°, a series of measurements of the temperature and pressure being made. From the observed values of the quotient $P/T$ it was found that decomposition of the vapour of tetrasilane commenced at 220—230°. The reaction products were not examined, but they probably consist of simpler and of more complex saturated hydrides. At considerably higher temperatures it is known that decomposition into silicon and hydrogen is complete.

A few experiments were made on the reactions of tetrasilane, but the products are of such low volatility and complexity that they were not fully characterised. Tetrasilane did not react with pure chloroform or bromoform even on prolonged storage at room temperature or on heating to 50° for 1 hour in a sealed tube with an excess of either reagent. However, in the presence of 1 or 2% of anhydrous aluminium chloride considerable halogenation of the tetrasilane took place in a few hours. The products were all of low volatility and the mixture produced was believed to be very complex. So far it has proved possible to isolate only methylene chloride and bromide as two of the most volatile products of the two reactions.

With iodoform, however, tetrasilane reacts in the absence of a catalyst. A small quantity of tetrasilane (0·6 g.) was sealed up with some iodoform (0·8 g.). At room temperature some of the iodoform dissolved to give a yellow solution. Heating to 60° for 10 minutes only dissolved more iodoform, which recrystallised on cooling. No reaction was apparent on a further 15 mins.' heating to 65°. After ten days at room temperature all the iodoform had reacted, and a small amount of silicon tetraiodide had been formed and was identified by crystal form and m. p. The other products were liquid, colourless, and of low volatility; they were spontaneously inflammable, burning with a flame evolving clouds of iodine vapour. Tetrasilane was also shown to react slowly with phosphorus tri-iodide. A sample of tetrasilane, sealed up with some of the tri-iodide and heated to 100° for 15 minutes, produced hydrogen and, in addition to some unchanged tetrasilane, a less volatile fraction consisting of a spontaneously inflammable, colourless liquid which evolved clouds of iodine vapour on combustion. These last two reactions obviously produce iodotetrasilanes whose characterisation must await more refined technique.

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## 252. *The Structure of Adreno-cortical Metabolites: $\Delta^{9:11}$-Androstene-3 : 17-dione.*

By C. W. SHOPPEE.

11(β)-Hydroxy*iso*androsterone (II), obtained from the adrenal cortex of cattle, and 11(β)-hydroxyandrosterone (VIII), isolated by Mason and Kepler (*J. Biol. Chem.*, 1945, **161**, 235) from the urine of human subjects with adrenal dysfunction, by dehydration afford epimeric $\Delta^{9:11}$-androsten-3-ol-17-ones (III) (IX), which are oxidised by chromium trioxide to $\Delta^{9:11}$-androstene-3 : 17-dione (IV). The $\Delta^{11}$-androsten-3(α)-ol-17-one (VII), isolated by Fieser *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 582) from the urine of a girl suffering from an adreno-cortical tumour furnishes by oxidation a diketone, isomeric and not identical with (IV), which is regarded as $\Delta^{11}$-androstene-3 : 17-dione (X). The origin of 17-ketosteroids in general and of (VII) and (VIII) in particular is briefly considered.

SOME years ago the writer described (*Helv. Chim. Acta*, 1940, **23**, 740) a degradation of the pentol (I; Reichstein's substance A) isolated from the adrenal cortex of cattle; oxidation of (I) with periodic acid gave androstane-3(β) : 11(β)-diol-17-one (II), a compound also isolated from the cortex (Reichstein and von Euw, *ibid.*, 1938, **21**, 1197, 1201), and dehydration of the 3-monoacetate of this with hydrochloric acid eliminated the 11(β)-hydroxyl group to afford $\Delta^{9:11}$-androsten-3(β)-ol-17-one acetate (III; R = Ac), which by hydrogenation and acetylation furnished androstane-3(β) : 17(α)-diol diacetate.

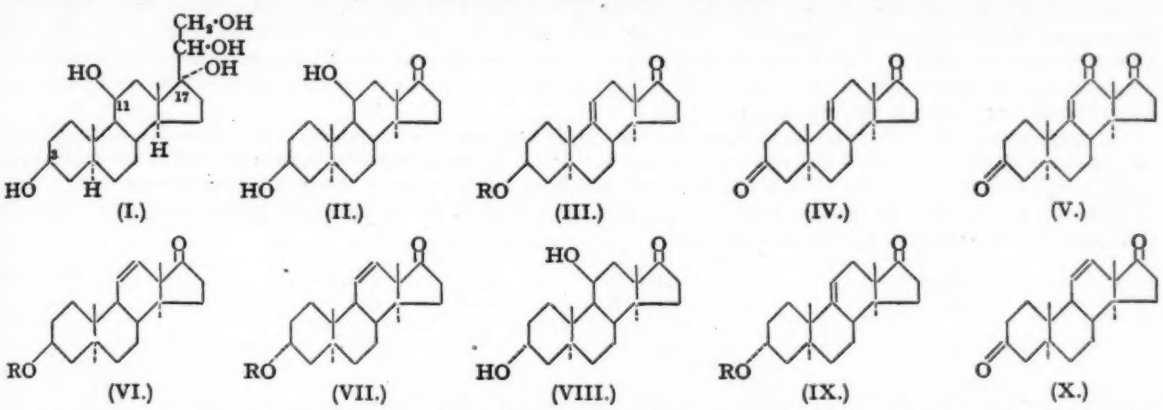
The acetate (III; R = Ac) was originally assigned the $\Delta^{11}$-structure (VI; R = Ac), but subsequent work * indicates by analogy that the $\Delta^{9:11}$-formulation now employed is correct.

The acetate (III; R = Ac) has been hydrolysed to the free *hydroxy-ketone* (III; R = H) and this converted by oxidation with chromium trioxide to $\Delta^{9:11}$-*androstene*-3 : 17-*dione* (IV; m. p. 154°, $[\alpha]_D^{14°}$ +156° ±2·5°, $[\alpha]_{5461}^{14°}$ +183° ±2·5°). The diketone (IV) was accompanied by traces of a higher-melting substance which may be $\Delta^{9:11}$-androstene-3 : 12 : 17-trione (V); if the identity of this by-product could be established as (V), this would provide further evidence in support of the position assigned to the double bond in (III) and (IV).

In 1941, Wolfe, Fieser, and Friedgood (*J. Amer. Chem. Soc.*, 1941, **63**, 582) isolated from the urine of a girl suffering from a recurrent adreno-cortical tumour an androstenolone which they suggested might be the $C_3$-epimeride (VII; R = H) of the supposed hydroxy-ketone (VI; R = H), since by hydrogenation it furnished

* The compound obtained by dehydration of 11(β)-hydroxyprogesterone with hydrochloric acid and originally described as $\Delta^{11}$-progesterone (Shoppee, *Helv. Chim. Acta*, 1941, **24**, 351) is to be regarded as $\Delta^{9:11}$-progesterone because it is different from the true $\Delta^{11}$-progesterone obtained by pyrolysis of 12(β)-benzoxyprogesterone (Reichstein and Hegner, *ibid.*, 1943, **26**, 715). Further, dehydration of methyl 11(β)-hydroxycholanate (Reichstein and Reich, *ibid.*, 1943, **26**, 568) and of methyl 3(α) : 11(β)-dihydroxycholanate (Reichstein and Lardon, *ibid.*, p. 586) with hydrochloric acid produces only traces of the $\Delta^{11}$-esters, the main products being the $\Delta^{9:11}$-esters whose structures were proved by conversion with perbenzoic acid into the known 9 : 11-oxidoesters; compare also Reichstein and Lardon (*ibid.*, 1945, **28**, 1420).

androstane-3(α) : 17(α)-diol; they also suggested the possibility that the preliminary hydrolysis with hydrochloric acid, to which the urine had been subjected, had caused dehydration of a cortical metabolite (VIII).




The level of urinary 17-ketosteroids is largely unaltered by castration, but rises when the adrenal gland is affected by benign hyperplasia or by malignant tumour of the cortex; further, in Addison's disease, which results from destruction of the adrenal gland, generally following tubercular infection, abnormally low values are found. It therefore seems probable that urinary 17-ketosteroids arise principally from the adrenal cortex rather than the gonads, and represent end-products of the metabolism of the adrenal cortical hormones and their congeners.

Accordingly, it appeared of interest to attempt to establish the structure of the androstenolone of Wolfe, Fieser, and Friedgood, and this was suggested to Professor Fieser in 1941. Various circumstances combined to preclude dealing with the matter until lately; in the meantime Mason and Kepler (*J. Biol. Chem.*, 1945, **161**, 235) have isolated androstane-3(α) : 11(β)-diol-17-one (VIII) from the urine of 3 out of 6 women suffering from tumour of the adrenal cortex and from the urine of 3 out of 4 patients suffering from bilateral andrenal cortical hyperplasia,* and have established its constitution by oxidation with chromium trioxide to androstane-3 : 11 : 17-trione. Thus the 11(β)-hydroxyl group survived the preliminary hydrolysis with N-hydrochloric acid, although Wolfe, Fieser, and Friedgood, using only approximately 0·1N-acid, had been unable to detect (VIII). Nevertheless it was anticipated that (VIII) by loss of the 11(β)-hydroxyl group might yield Wolfe, Fieser, and Friedgood's compound (VII; R = H, m. p. 181—183°, $[\alpha]_D^{26\cdot5°}$ +122° ±2°; R = Ac, m. p. 178—180°, $[\alpha]_D^{26\cdot5°}$ +114° ±5°), but application by Mason and Kepler of the writer's method for the elimination of the 11(β)-hydroxyl group characteristic of the cortical substances furnished an isomeric androstenolone (m. p. 189—190°, $[\alpha]_D^{28°}$ +140 ±2°; acetate, m. p. 190—192°, $[\alpha]_D^{25°}$ +135° ±3°). Since this new isomeride by hydrogenation afforded androstane-3(α) : 17(α)-diol, the isomerism is conditioned solely by the location of the double bond. Through the kindness of Dr. H. M. Mason, who provided 15 mg. of (VIII), it has now been shown that the androstenolone of Mason and Kepler is the $C_3$-epimeride (IX; R = H) of the cortical degradation product (III; R = H) because by oxidation with chromium trioxide it yields the same unsaturated diketone (IV).

Quite recently, Miller, Dorfman, and Sevringhaus (*Endocrinology*, 1946, **38**, 19) have isolated the cortical metabolite (VIII) from a pathological urine which had not been subjected to preliminary acid hydrolysis. Dorfman, Schiller, and Sevringhaus (*ibid.*, 1945, **37**, 262) had previously obtained from hydrolysed urine of the same patient an androsten-3(α)-ol-17-one acetate, m. p. 179—182°, which was considered possibly to be identical with the compound (VII; R = Ac), m. p. 178—180°, of Wolfe, Fieser, and Friedgood; the m. p. of this acetate has now been raised to 188·5—189°, and it has been shown to be identical with the acetate (IX; R = Ac), m. p. 190—192°.

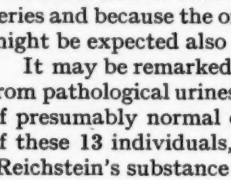
With the kind co-operation of Professor Fieser, who provided material furnishing 6 mg. of (VII; R = H), a corresponding oxidation has been carried out on this compound. The 3(α)-benzoyl group of the benzoate (VII; R = Bz) showed unexpected resistance to hydrolysis by potassium carbonate, and in part survived treatment with cold N/5-sodium hydroxide; oxidation of (VII; R = H) with chromium trioxide gave an *androstene*-3 : 17-*dione*, m. p. 145—146°, which is provisionally regarded as (X), although location of the double bond at other positions, *i.e.*, $\Delta^6$ or $\Delta^7$, is not excluded by the chemical evidence adduced by Wolfe, Fieser, and Friedgood in respect of its precursor (VII; R=H). The new diketone gives little or no m. p. depression on admixture with Δ⁹:¹¹-androstene-3 : 17-dione (IV), but its specific rotation, $[\alpha]_D^{15°}$ + 141° ± 3·5°, $[\alpha]_{5461}^{15°}$ + 170·5° ± 3·5°, clearly indicates that it is different from this substance.

Since progesterone (XI; R = H) (Venning and Brown, *Endocrinology*, 1937, **21**, 711) and deoxycorticosterone (XI; R = OH) (Westphal, *Z. physiol. Chem.*, 1942, **273**, 13; Hoffman, Kazmin, and Browne, *J. Biol. Chem.*, 1943, **147**, 259) undergo metabolic reduction to pregnane-3(α) : 20(α)-diol (XII) (rings A/B, *cis*), the

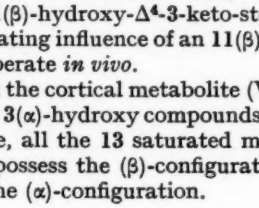
* Note (added June 14th, 1946) : Mason (*J. Biol. Chem.*, 1946, **162**, 745) reports the isolation of (VIII) from the urine of normal men, but in about one fifth the quantity obtained from pathological urines.

metabolic production of the androstane derivative (VII; R = H) (cf. also VIII) (rings A/B, *trans*) may indicate that it originates from an 11(β)-hydroxy-cortical hormone, *e.g.*, corticosterone (XIII) or 17(α)-hydroxycorticosterone (XIV), because it is known (Kendall, Mason, Hoehn, and McKenzie, *J. Biol. Chem.*, 1937, **120**, 719; Steiger and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 817; 1938, **21**, 161, 828; cf. Shoppee, *ibid.*, 1941, **24**, 351) that reduction *in vitro* of 11(β)-hydroxy-$\Delta^4$-3-keto-steroids furnishes exclusively compounds of the androstane series and because the orientating influence of an 11(β)-hydroxyl-group on the stereochemical course of reduction might be expected also to operate *in vivo*.

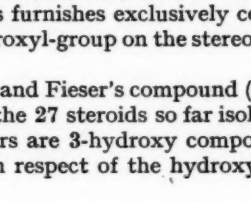
It may be remarked that the cortical metabolite (VIII) and Fieser's compound (VII; R = H), both derived from pathological urines, are 3(α)-hydroxy compounds; of the 27 steroids so far isolated from the adrenal cortex of presumably normal cattle, all the 13 saturated members are 3-hydroxy compounds of the *allo*-series, but, of these 13 individuals, 12 possess the (β)-configuration in respect of the hydroxyl group at $C_3$ and one only (Reichstein's substance C) the (α)-configuration.



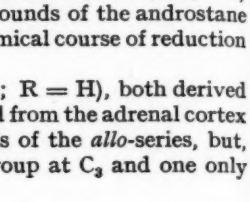
(XI.)



(XII.)



(XIII.)



(XIV.)

## Experimental.

(All m. ps. were determined thermoelectrically on a Kofler block and are corrected: limit of error ±2°. All solvents used for chromatographic analysis were rigorously purified and dried.)

$\Delta^{9:11}$-*Androsten*-3(β)-*ol*-17-*one* (III; R = H).—The acetate (III; R = Ac) (27·5 mg.) was dissolved in methanol (2 c.c.), a solution of potassium carbonate (23 mg.) in water (0·5 c.c.) added, and the mixture kept for 48 hours at 20°. The long thin plates which separated were filtered off, washed with a little water, and dried (12 mg.; m. p. 169—172°). The material sublimed readily in a molecular flask at 130° (bath temp.)/0·01 mm., and was recrystallised from dilute methanol to give 9 mg. of $\Delta^{9:11}$-*androsten*-3(β)-*ol*-17-*one*, m. p. 170—172·5°, $[\alpha]_D^{13°}$ +125·5° ±2°, $[\alpha]_{5461}^{13°}$ +161° ±2° (*c*, 0·534 in ethanol) [Found (after drying at 40°/0·01 mm.): C, 79·40; H, 9·88. $C_{19}H_{28}O_2$ requires C, 79·13; H, 9·78%]. The aqueous methanol filtrate and mother liquor were united (methanol removed under reduced pressure) and extracted with ether. The extract was washed with water, dried ($Na_2SO_4$), and concentrated to afford 13 mg. of the hydroxy-ketone, m. p. 169—171°.

$\Delta^{9:11}$-*Androstene*-3:17-*dione* (IV).—(a) *From* (III: R = H). The hydroxy-ketone (III; R = H) (18 mg., m. p. 169—172°) was dissolved in pure acetic acid (0·35 c.c., redistilled over chromium trioxide), and a 2% solution of chromium trioxide in acetic acid (0·35 c.c. ≡ 7 mg. $CrO_3$) added. The solution became turbid, but was clear after 16 hours at 15°. After complete removal of acetic acid under reduced pressure at 30°, a few drops of water were added and the product was extracted with ether; the aqueous solution contained an excess of chromium trioxide. The ethereal extract was washed with N-sulphuric acid, water, N-sodium carbonate, and again with water, dried briefly ($Na_2SO_4$), and evaporated. The crystalline residue separated from the ether–pentane in thin prisms, which were washed with ether–pentane (1 : 1) and pentane: 15 mg., m. p. 150—155° to a turbid melt clearing at about 160°. The mother liquor by evaporation gave 2 mg. of non-crystalline material.

The crystalline product (15 mg.) was purified by dissolution in benzene–pentane (1 : 2; 2 c.c.) and filtration through a column of aluminium oxide (Merck–Brockmann, Activity III *; 0·5 g.) prepared in pentane (5 c.c.). Each eluate (3 c.c.) was evaporated, the residue was crystallised from ether–pentane, and the crystals were washed with ether–pentane and pentane.

| Fraction. | Eluant. | Eluate. |
|---|---|---|
| 1—3 | Pentane | — |
| 4—9 | Benzene–pentane (1 : 1) | Prisms, m. p. 152—154°. |
| 10 | Benzene | ,, ,, 153—154°. |
| 11, 12 | ,, | Traces of cryst. material, m. p. 150—154°. |
| 13 | Ether–benzene (1 : 9) | — |
| 14 | ,, (1 : 4) | Little cryst. material, m. p. 190—195° after softening from 180°. |
| 15 | ,, (1 : 1) | Trace of cryst. material. |
| 16 | Ether | — |
| 17 | Acetone–ether (1 : 1) | — |

Fractions 4—12 were united and recrystallised from ether–pentane to furnish $\Delta^{9:11}$-*androstene*-3:17-*dione* (10 mg.); two crystal habits were observed, large flat plates and long thin prisms, both melting at 153—154°, the melt recrystallising at 148° and remelting at 154°, $[\alpha]_D^{14°}$ +156° ±2·5°, $[\alpha]_{5461}^{14°}$ +183° ±2·5° (*c*, 0·404 in ethanol) [Found (after drying at 40° in a high vacuum): C, 79·34; H, 9·34. $C_{19}H_{26}O_2$ requires C, 79·67; H, 9·15%].

(b) *From* (VIII). Androstane-3(α):11(β)-diol-17-one (VIII) (14 mg., m. p. 198°), dehydrated by the procedure described by Mason and Kepler (*loc. cit.*), furnished $\Delta^{9:11}$-androsten-3(α)-ol-17-one (IX; R = H) (2 mg.), hexagonal prisms, m. p. 189—190° and its acetate (IX; R = Ac) (13 mg.), long thin prisms, m. p. 192—193°. The acetate (13 mg.) by hydrolysis gave the free hydroxy-ketone (11·5 mg.), m. p. (crude) 188—190°. The hydroxy-ketone (13·5 mg.) was dissolved in pure acetic acid (0·25 c.c., redistilled over chromium trioxide) and treated with a 2% solution of chromium trioxide in acetic acid (0·25 c.c. ≡ 5 mg. $CrO_3$); the solution remained clear and was kept for 16 hours at 20°. Working up showed an excess of chromium trioxide to be present, and afforded a crystalline residue (12·7 mg.), m. p. (crude) 145—151°. This residue was dissolved in benzene–pentane (1 : 1) (0·5 c.c.) and introduced on to a column of aluminium

* According to the scale suggested by Brockmann and Schodder (*Ber.*, 1941, **74**, 73).

oxide (Merck–Brockmann, activity III; 0·5 g.) prepared in pentane (5 c.c.). Elution with 7 × 2 c.c. portions of benzene–pentane (1 : 1) and 2 × 2 c.c. portions of benzene yielded $\Delta^{9:11}$-androstene-3:17-dione (8·3 mg.), thin prisms from ether–pentane, m. p. 153—154°, mixed m. p. with the specimen prepared by method (a), 153—154°, the melt resolidifying at 150° and remelting at 154°, $[\alpha]_D^{15°}$ +154·5° ±2°, $[\alpha]_{5461}^{15°}$ +181·3° ±2° (*c*, 0·634 in ethanol) [Found (after sublimation at 140°/0·01 mm.): C, 79·50; H, 9·20%]. Elution with ether–benzene (1 : 4) gave traces of a substance, crystallising from ether–pentane in plates, m. p. 195—197°, which may be $\Delta^{9:11}$-androstene-3:12:17-trione; the quantity was insufficient for analysis.

*$\Delta^{11(12)}$-Androsten-3(a)-ol-17-one* (VII; R = H).—(*a*) The acetate (VII; R = Ac) (2·6 mg.) was dissolved in methanol (0·5 c.c.), a solution of potassium carbonate (2·5 mg.) in water (0·05 c.c.) was added, and the mixture kept at 20° for 48 hours. After evaporation under reduced pressure, the residue was extracted with ether and furnished a mixture of the hydroxy-ketone and the unhydrolysed acetate.

(*b*) The benzoate (VII; R = Bz) (3·4 mg.; m. p. 164°) was similarly treated, but crystallised out in long prisms, m. p. 164—165°, which could not be redissolved by gentle warming. After addition of methanol (0·5 c.c.), the mixture was therefore refluxed on the steam-bath for 1 hour. Working up gave a residue which crystallised on being kept overnight, m. p. 140° approx. This product, consisting of the hydroxy-ketone and unhydrolysed benzoate, was united with the crude hydroxy-ketone obtained under (*a*) to give 6 mg. of material, which was introduced in benzene (0·25 c.c.) on to a column of aluminium oxide (Merck–Brockmann, activity III; 0·5 g.) prepared in pentane (5 c.c.). Elution with benzene–pentane (1 : 1) (5 × 2 c.c.) and with benzene (3 × 2 c.c.) removed all unhydrolysed acetate and benzoate. Crystallisation of these united fractions from ether–pentane furnished prisms, m. p. 160—162°, m. p. 162—164° on admixture with the benzoate; the crystals and the mother liquor gave 4 mg. of unhydrolysed material, which was again submitted to hydrolysis (*vide infra*). Elution of the column with ether–benzene (1 : 1) (2 × 2 c.c.) and with ether (3 × 2 c.c.) yielded fractions which crystallised spontaneously by evaporation; they were united and the residue recrystallised from ether–pentane to afford 1·4 mg. of long needles, m. p. 178—180°, m. p. 178—181° on admixture with a genuine specimen of the hydroxy-ketone (VI; R = H).

The unhydrolysed material (4 mg.) was dissolved in methanol (1·5 c.c.), N-sodium hydroxide (0·3 c.c.) added, and the mixture kept for 16 hours at 20°. After addition of a few drops of water, the solution was saturated with carbon dioxide, methanol removed under reduced pressure, and the suspension extracted with ether. The extract was washed with a little water, dried briefly ($Na_2SO_4$), and evaporated to yield an oil (3 mg.) which crystallised partially. This material was chromatographed as described above on aluminium oxide (0·3 g.). Elution with benzene–pentane (1 : 1) gave only mere traces of crystalline material; the first benzene eluate gave a small crystalline residue, which consisted of unhydrolysed benzoate, m. p. 164—165° after recrystallisation from ether–pentane. m. p. 135—140° on admixture with the hydroxy-ketone. Subsequent benzene eluates yielded no residue. Elution with ether–benzene (1 : 1) furnished a residue which crystallised spontaneously, m. p. 170—172°, whilst the first ether eluate similarly afforded crystals, m. p. 172—173°; these fractions were united and recrystallised from ether–pentane to give the hydroxy-ketone (VII; R = H) (1·6 mg.), m. p. 174°, resolidifying immediately and remelting at 174°, and giving no depression on admixture with a genuine specimen, m. p. 178°. Subsequent ether eluates yielded no residue.

*$\Delta^{11(12)}$-Androstene-3:17-dione* (X).—The hydroxy-ketone (VII; R = H) obtained by the foregoing hydrolyses (3 mg.) together with the genuine specimen supplied by Professor Fieser (m. p. 178—181°; 3·5 mg.) was dissolved in acetic acid (0·12 c.c., redistilled over chromium trioxide), and a 2% solution of chromium trioxide in acetic acid (0·12 c.c. ≡ 2·4 mg. $CrO_3$) added. The turbid solution became clear in about ½ hour, and was kept for 16 hours at 15°. After complete removal of acetic acid under reduced pressure at 30°, a few drops of water were added, and the product was extracted with ether; the aqueous solution contained an excess of chromium trioxide. The ethereal extract was washed with N-sulphuric acid, water, N-sodium carbonate, and again with water, dried briefly ($Na_2SO_4$), and evaporated to furnish a crystalline residue (6 mg.), m. p. 139—141° after some softening. This product was dissolved in benzene (0·25 c.c.) and analysed chromatographically on a column of aluminium oxide (Merck–Brockmann, activity III; 0·25 g.) prepared in pentane (5 c.c.) as follows:

| Fraction. | Eluant. | Volume, c.c. | Eluate. |
|---|---|---|---|
| 1 | Pentane | 5 | Trace of oil. |
| 2 | ,, | 5 | — |
| 3 | Benzene–pentane (1 : 9) | 1 | — |
| 4 | ,, (1 : 4) | 1 | — |
| 5 | ,, (1 : 2) | 1 | Traces of cryst. material. |
| 6 | ,, (1 : 1) | 2 | Cryst. spontaneously, m. p. 144—146°. |
| 7 | ,, (1 : 1) | 2 | ,, ,, ,, 140—142°. |
| 8 | ,, (1 : 1) | 2 | ,, ,, ,, 140—142°. |
| 9 | Benzene | 2 | ,, ,, ,, 139—141°. |
| 10 | ,, | 2 | — |
| 11 | Ether | 5 | — |

Fractions 5—9 were united to give 5 mg. of material, which by recrystallisation from ether–pentane furnished *$\Delta^{11(12)}$-androstene-3:17-dione* (3 mg.) as clusters of prisms, m. p. 145—146°, recrystallising at once on slight cooling and remelting at 146°. On admixture with $\Delta^{9:11}$-androstene-3:17-dione, m. ps. 143—146° and 143—147° with immediate crystallisation of the melt on slight cooling and remelting at 146—147° were observed, so that these substances give little or no depression. The specific rotation, however, confirms their non-identity: $[\alpha]_D^{15°}$ +141·5° ±3·5°, $[\alpha]_{5461}^{15°}$ +170·5° ±3·5° (*c*, 0·2932 in ethanol). For analysis, the material used for the determination of the specific rotation was recovered and sublimed at 130°/0·001 mm. (Found: C, 79·20; H, 9·24. $C_{19}H_{26}O_2$ requires C, 79·67; H, 9·15%).

The author wishes to thank Professor L. F. Fieser, Harvard University, and Dr. H. L. Mason, The Mayo Clinic, Rochester, Minnesota, for their kind co-operation, and Professor T. Reichstein, Basle University, for the gift of a quantity of aluminium oxide (Merck–Brockmann); he also acknowledges the generous support of the British Empire Cancer Campaign and the Jane Coffin Childs Memorial Fund.

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# 253. *Steroids and the Walden Inversion. Part I. Derivatives of Androstane and Cholestane.*

By C. W. Shoppee.

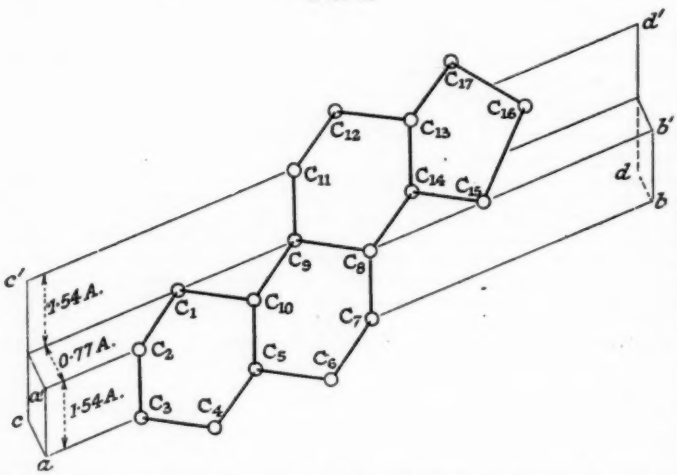
The principles enunciated by Cowdrey, Hughes, Ingold, Masterman, and Scott (*J.*, 1937, 1252) are applied to elucidate the steric orientation of replacement reactions occurring at saturated carbon atoms of the steroid nucleus.

The stereochemistry of androstane is discussed in relation to the geometry of the transition state in bimolecular steroid nuclear substitution; it is shown that the stereochemical arrangement of the steroid nucleus intrinsically favours the formation of a transition state of linear type and so reinforces the conclusion, reached on the basis of the exclusion principle, that in the replacement of ·Hal by ·OR inversion of configuration is the rule. The so-called "α"- and "β"-cholestanyl chlorides are shown to possess the constitutions 3(β)-chlorocholestane and 3(α)-chlorocholestane respectively, and the above conclusion is applied further in Section (*a*) to the extensive body of data available in respect of substitution at $C_3$ in saturated steroids, *e.g.*, derivatives of androstane and cholestane.

In Section (*b*), the orientation rules of Cowdrey *et al.* (*loc. cit.*) for the replacement of ·OR by ·Hal are applied to substitution at $C_3$ in saturated steroids, to furnish a picture which is not only self-consistent, but consistent also with the configurations assigned in Section (*a*).

During the last decade, the work of Ingold, Hughes, and their collaborators has thrown much light on the stereochemical course of substitution at a saturated carbon atom. It seems appropriate to attempt to apply the principles and diagnostic rules enunciated by these workers to some simple steroid substitution reactions with a view to assigning configurational relationships.

Fig. 1.




*The androstane nucleus (omitting the angular methyl groups) seen in isometric projection at 22·5°.*

As compared with simple saturated compounds of the type $CHR_1R_2R_3$, the polycyclic steroid nucleus offers both intrinsic advantages and disadvantages. Thus, whereas in molecules of the type $CHR_1R_2R_3$ sign of rotation is a direct criterion of the stereochemical arrangement, and the numerical value of the rotation an index of stereochemical purity, in steroid molecules, because of the multiplicity of asymmetric centres contributing to the observed rotation, inversion of configuration at one of these centres may cause no change in sign of rotation and may alter the numerical value by a few degrees only; the application of superposition rules to molecular rotation values, when available, may, however, afford collateral evidence of configuration. On the other hand, because of the geometrical isomerism inherent to a cyclic structure, epimerides are distinct and often well-known compounds, so that inversion must furnish one and retention of configuration must yield the other, whilst racemisation must lead to production of both epimerides, and, if extensive, should render possible their isolation.

*The Geometry of the Steroid Nucleus.*—Since the conclusions of Ingold, Hughes, and their co-workers as to the course of bimolecular substitution reactions at saturated carbon atoms are based partly on an examination of the geometrical form and energy of the transition state, it seems desirable to examine briefly what modifications, if any, are introduced when the substitution reaction occurs at a saturated carbon atom forming part of the steroid nucleus.

The androstane molecule is a relatively flat structure. There is much evidence available (Ruzicka, Furter, and Thomann, *Helv. Chim. Acta*, 1933, **16**, 216; Ruzicka, Goldberg, Meyer, Brungger, and Eichenberger, *ibid.*, 1934, **17**, 1407; Ruzicka, Goldberg, and Wirz, *ibid.*, 1935, **18**, 61; Windaus, *Annalen*, 1926, **447**, 233; Wieland and Dane, *Z. physiol. Chem.*, 1933, **216**, 91; Dimroth and Jonsson, *Ber.*, 1941, **74**, 520; Giacomello, *Gazzetta*, 1939, **69**, 790; Bernal, Crowfoot, and Fankuchen, *Phil. Trans.*, 1940, *A*, **239**, 135; Carlisle and Crowfoot, *Proc. Roy. Soc.*, 1945, *A*, **184**, 64) to show that the four constituent rings are linked by *trans*-unions. The essential carbon-ring structure is thus to be regarded as constructed on two parallel planes separated by a distance of about 0·77 A.

The first plane *aa'bb'* contains the carbon atoms conventionally numbered $C_2$, $C_3$, $C_5$, $C_{10}$, $C_7$, and $C_8$, and $C_{15}$ probably lies in or very near it; the second plane *cc'dd'*, situated to the rear of the first, contains the carbon atoms $C_9$, $C_{11}$, $C_{13}$, and $C_{14}$, whilst $C_{16}$ probably lies in or very near it. The angular methyl groups attached to $C_{10}$ and $C_{13}$ are omitted from Fig. 1; *trans*-fusion of rings A/B and C/D necessitates that the

angular methyl groups are similarly orientated, and they are by convention * regarded as projecting forward from the planes *aa'bb'* and *cc'dd'*. It may, however, be pointed out that the absolute configuration of no single centre of asymmetry has yet been determined despite the contrary statement of Bergmann (*J. Soc. Chem. Ind.*, 1939, **58**, 512), so that the stereochemical arrangement of the androstane molecule and of the natural steroids of the $C_5$-*allo*-series (rings A/B, *trans*) may actually be the mirror image of that depicted in Fig. 1. With this reservation it seems certain from the crystallographic studies summarised by Bernal, Crowfoot, and Fankuchen (*loc. cit.*) that the structure depicted in Fig. 1 represents the actual spatial arrangement of the steroid nucleus for androstane and its derivatives in the crystalline state.

Examination of a mechanical model of the androstane molecule (cf. Fig. 1), in which both ring A and ring B are chair forms, indicates that whilst rings B and C cannot undergo modification on account of double-locking by *trans*-union with rings A and C and rings B and D respectively, ring A can undergo conversion into a boat form by relative motion of carbon atoms $C_2$ and $C_3$ whereby $C_3$ and $C_{10}$ become the ends of the boat without disturbance of the remainder of the tetracyclic structure. It is therefore necessary to inquire whether such a modified form of ring A can make a contribution to the stereochemistry of androstane and its derivatives in the liquid state or in solution.

There is no convincing evidence that the boat form of *cyclo*hexane itself, which is stereochemically equivalent to a plane ring, has any individuality. Thus comparison of the entropies derived from thermal data over the range 10—293° K. with those computed from molecular and spectroscopic data suggests that *cyclo*hexane, as a result of the mutual repulsions of the electrons involved in the C–H bonds, exists only as the chair form (Aston, Schumann, Fink, and Doty, *J. Amer. Chem. Soc.*, 1943, **65**, 341) (in regard to the decalins, see Bastiansen and Hassel, *Nature*, 1946, **157**, 765). From the chemical point of view, the chair form of *cyclo*hexane, being rigid, should afford two isomeric mono-substitution products; but it has been shown in an appropriate case by Wightman (*J.*, 1926, 2543) that only a single individual can be isolated, so that interconversion of the isomerides must occur in solution even if succeeded by preferential separation of one individual on packing into the crystal lattice. A very rough estimate of the height of the energy barrier opposing such interconversion (chair ⟶ boat ⟶ chair) can be made on the assumption that the principal contributions are the energies required (*a*) to overcome the mutual repulsions of the hydrogen atoms, (*b*) to deform two tetrahedral C–C–C angles to 120°, and (*c*) to accomplish the concomitant deformation of four C–C–H angles. Component (*a*) may be evaluated at 6 kg.-cals. mole$^{-1}$ for the twelve hydrogen atoms in *cyclo*hexane, since the energy barrier, which opposes free rotation about their common axis of the methyl groups in ethane and necessitates that the structure of minimum energy is that with maximum separation of the hydrogen atoms, *i.e.*, the *trans*-configuration, has a value of 3 kg.-cals. mole$^{-1}$ (Kemp and Pitzer, *J. Amer. Chem. Soc.*, 1937, **59**, 276; cf. Pitzer and Gwinn, *ibid.*, 1941, **63**, 33). Component (*b*) may approximately be assessed using the transformation formula $E_{(\theta-2\alpha)} = E_\theta \cdot \cos^2\alpha$ given by Skinner (*Trans. Faraday Soc.*, 1945, **41**, 645); in each C–C bond strained through an angle $\alpha = 5°$ from the normal, we might expect the bond energy to be increased by an amount given by $\frac{L}{2}/\cos^2 5° = 1{\cdot}01\,\frac{L}{2}$ where $L$ = the heat of sublimation of diamond, so that the energy required to effect deformation will be $1{\cdot}01\,\frac{L}{2} - \frac{L}{2}$ or about 1% of $\frac{L}{2}$. Current values of $L$ range from 125 to 170 kg.-cals. mole$^{-1}$, and afford a value of 0·6 to 0·9 kg.-cals. for each C–C bond or 2·4 to 3·6 kg.-cals. for deformation of two tetrahedral angles to 120°. Component (*c*) is difficult to estimate; but if, using the geometrical expression $\cos\theta = \frac{1}{4}\{\sqrt{\cos^2\beta + 8} - \cos\beta\}$ given by Becker and Thorpe (*J.*, 1920, 1579), we assume for an endocyclic C–C–C angle $2\theta = 120°$ that the exocyclic H–C–H angle $2\beta = 107°$, so that each C–H bond is strained through an angle $\alpha = \sim 1{\cdot}5°$, and apply Skinner's transformation formula taking the C–H bond energy as $56{\cdot}5 + \frac{L}{4}$ kg.-cals. mole$^{-1}$, it appears that the energy needed is about 0·1 kg.-cal., or ~0·5 kg.-cal.

* The convention adopted for the representation and description of substituted steroids is that proposed by Fieser ("The Chemistry of Natural Products Related to Phenanthrene," 2nd Edition, New York, 1937, pp. 398, 399; cf. Callow, *Ann. Reports*, 1938, **35**, 281) and extended by Reichstein and Shoppee ("Vitamins and Hormones," New York, 1943, p. 349); position is specified by the number of the nuclear carbon atom bearing the substituent, configuration by the suffix (α) or (β). As emphasised by Callow (*loc. cit.*) the parentheses are important but for a different reason; they not only afford differentiation from provisional trivial indices, but also indicate a definite stereochemical orientation. Thus the position and configuration of the hydroxyl group common to cholesterol, dihydrocholesterol, and coprostanol (coprosterol) is defined by the expression 3(β); this hydroxyl group lies on the same side of the plane *aa'bb'* (Fig. 1) as does the angular methyl group attached to $C_{10}$, and this is conventionally represented by a full-line bond. In *epi*-cholesterol, *epi*dihydrocholesterol, and *epi*coprostanol (*epi*coprosterol) the position and configuration of the hydroxyl group is defined by the expression 3(α); the hydroxyl group and the angular methyl group attached to $C_{10}$ lie on opposite sides of the plane *aa'bb'*, and this is conventionally expressed by use of a broken-line bond. The evidence in favour of these orientations is summarised by Ruzicka, Furter, and Goldberg (*Helv. Chim. Acta*, 1938, **21**, 498).

For substituents in steroid side chains, *e.g.*, secondary or tertiary but not primary hydroxyl groups, position is specified by the number of the carbon atom bearing the group in question, but since stereoisomerism is now no longer geometrical in character but of the classical tartaric acid type a definite spatial orientation cannot in general be assigned. The indices α and β *without* parentheses, adjacent to and following a position numeral, *e.g.*, 20α, 20β, should be employed, but *n*- and *iso*- have also been used. These suffixes without parentheses serve solely to distinguish stereoisomerides without any spatial implication; and since here suffix assignment is arbitrary, compounds labelled, *e.g.*, 20β, will not necessarily possess corresponding configuration at $C_{20}$ (cf. Prins and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 1490).

for deformation of four C–C–H angles. Summation of components (*a*), (*b*), and (*c*) gives the approximate height of the energy barrier as 9—10 kg.-cals. mole$^{-1}$ in *cyclo*hexane.

Since the chair–boat transformation of ring A of androstane can apparently occur independently of the attached fused-ring system, the height of the energy barrier here should be of the same order of magnitude as for *cyclo*hexane; the value calculated is small compared with the activation energies of most chemical reactions, and the energy required appears to be derivable from thermal bombardment at ordinary temperatures. Stereochemistry deals with structures which retain individuality under such conditions; from the stereochemical point of view it is useless to attempt to distinguish between geometrical arrangements which are separated by energy hills so low that they will normally be traversed with great frequency in the liquid state or in solution. Very many $C_3$-substituted derivatives of androstane are known, but in no case have more than two individuals been reported. We conclude therefore that the possible boat form of ring A in androstane makes no contribution to the stereochemistry of this substance and its derivatives.

The nuclear carbon atoms of the androstane molecule lie in, or either side of, but never far away from, a common plane *ac'bd'* (Fig. 1) situated between the planes *aa'bb'* and *cc'dd'*. Since most of the substitution reactions to be considered later occur at $C_3$, we shall for the purpose of discussing the geometry of the transition state confine attention to this centre. Before the approach of a reagent Y in a bimolecular substitution of X, the situation may be approximately depicted as in Fig. 2; the bonds $C_2$–$C_3$ and $C_3$–$C_4$ will lie in, or nearly in, the common plane *ac'bd'* and are constrained by the geometry of the ring-system to remain in, or nearly in, this plane. During the attack, lateral to that plane, of the reagent Y, the bond $C_3$–H will suffer deformation, until, in the transition state, it too lies in or near the common plane *ac'bd'*. An idealised representation of the transition state is shown in Fig. 3; the substituting reagent Y, the saturated carbon atom $C_3$, at which substitution occurs, and the displaced atom X are collinearly arranged on a normal to the plane

FIG. 2.

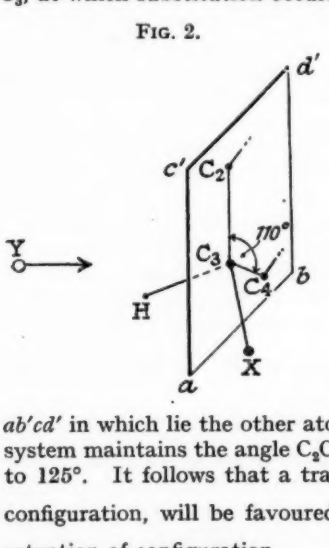



FIG. 3.

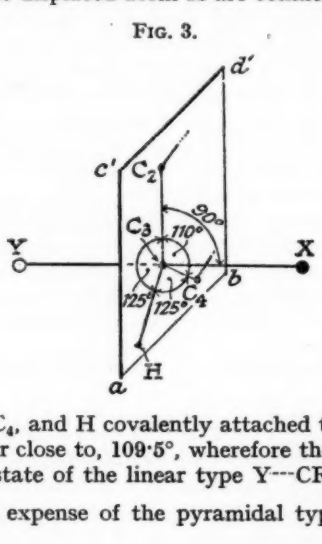
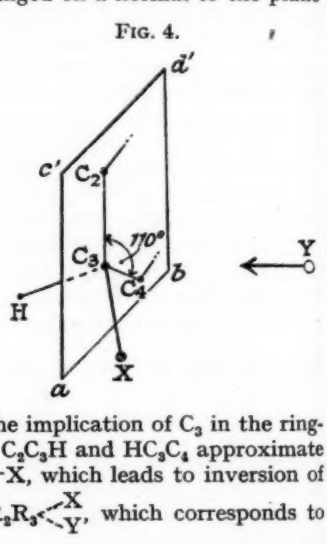



FIG. 4.




*ab'cd'* in which lie the other atoms $C_2$, $C_4$, and H covalently attached to $C_3$; the implication of $C_3$ in the ring-system maintains the angle $C_2C_3C_4$ at, or close to, 109·5°, wherefore the angles $C_2C_3H$ and $HC_3C_4$ approximate to 125°. It follows that a transition state of the linear type Y···$CR_1R_2R_3$···X, which leads to inversion of configuration, will be favoured at the expense of the pyramidal type $CR_1R_2R_3{<^{X}_{Y}}$, which corresponds to retention of configuration.

The approach of the reagent may, however, be not from the far side of the plane *ac'bd'*, as depicted in Fig. 2, but from the near side of the plane *ac'bd'*, as in Fig. 4, which would lead to a transition state of pyramidal type $CR_1R_2R_2{<^{X}_{Y}}$. It has been shown (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1256) by application of the exclusion principle that the energy of activation corresponding to a linear transition state is smaller than that corresponding to the pyramidal version; therefore the number of encounters of the type illustrated in Fig. 4 (which on the basis of chance would be expected to be approximately half the total number of encounters) coming to fruition will be much smaller than those of the type illustrated in Fig. 2, and, if the energy difference is sufficiently large, may become very small. In other words, in the absence of groups or structural features which on account of either unsaturation or charge tend strongly to influence the configuration of the transition state, a large proportion of encounters leading to reaction with inversion of configuration will succeed, whilst the great majority of those encounters which would lead to reaction with retention of configuration will fail. Hence for bimolecular substitutions ($S_N2$, $S_E2$) at positions 1, 2, 3, 4, 6, 7, 11, 12, and probably at positions 15, 16, and 17, of the androstane molecule predominant inversion should be the rule.

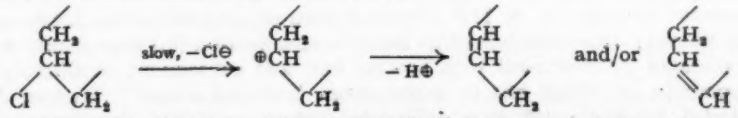
From the point of view of a reagent approaching through a surrounding medium, the most conspicuous feature differentiating the two sides of the lath-shaped androstane molecule will be the angular methyl groups at $C_{10}$ and $C_{13}$ projecting from the face. Except for positions 1 and 17 adjacent to the angular methyl groups and for position 11, which although not strictly adjacent to the $C_{10}$ methyl group is known experimentally to be subject to a quite extraordinary degree of steric hindrance, there will not be a conspicuous difference

between the face and the reverse of the androstane molecule, hence the foregoing conclusion should hold for the bimolecular replacement of both (α)- and (β)-orientated groups. For one of the three cases specified in which there is a marked difference, namely position 11, there is some independent corroboratory evidence available in support of this conclusion. The 11(α)- and 11(β)-bromo-12-keto-3(α)-acetoxycholanic esters of Seebeck and Reichstein (*Helv. Chim. Acta*, **1943**, **26**, 536) have both been shown (Gallagher and Long, *J. Biol. Chem.*, **1946**, **162**, 521, 533) to undergo alkaline hydrolysis under the same mild conditions with inversion to afford respectively the 3(α) : 11(β)- and 3(α) : 11(α)-dihydroxy-12-ketocholanic acids; the 11(α)-configuration is subject to marked steric hindrance by the angular methyl group attached to $C_{10}$ whilst the 11(α)-configuration is practically unhindered, and, as would be expected if replacement proceeds by the mechanism $S_N2$ in which steric effects operate, the reaction rates differ widely but the character of the substitution remains unaltered. There appears to be no evidence relating to positions 1 or 17; it may be pointed out that replacement reactions at $C_{17}$ involve a system analogous to the α-methyl*neo*pentyl group, and it is hoped to deal with these in a subsequent communication.

(*a*) *Replacement of* Cl *by* OR.—On the basis of extensive kinetic studies, Cowdrey, Hughes, Ingold, Masterman, and Scott (*J.*, 1937, 1252) state that " in all homogeneous substitutions of ·Hal by ·OR in (saturated) alkyl halides, no matter whether the mechanism is $S_N2$ or $S_N1$, the predominating orientation will be inversion." We therefore take as our reference substances the " α " and " β "-cholestanyl chlorides, which are typical, if complicated, alkyl halides containing besides the halogen only neutral saturated groups at the seat of substitution and formally comparable with β-*n*-octyl bromide, and consider their reactions with acetate ions in an ionising medium. The result of these reactions is described in the literature; a kinetic investigation to determine mechanism ($S_N1$ or $S_N2$) is unnecessary since it must be one or the other, and both lead to predominating inversion; further, in the present case this general conclusion is reinforced by the special conclusion reached above on grounds of steroid molecular geometry.

It has been shown by numerous methods that acid or alkaline hydrolysis of a carboxylic ester occurs by fission between the singly-bonded oxygen atom and the carbonyl group (cf. Watson, *Ann Reports*, 1940, **37**, 229 *et seq.*); unless special conditions are present, leading to suppression of acyl–oxygen fission (R–CO|O-steroid) and incursion of alkyl–oxygen fission [R–CO·O–|steroid (cf. Watson, *loc. cit.*, p. 230, footnotes 5 and *)] as in R·CO·O–C(C)(C)C —a structure which never appears in steroid esters at the nuclear positions under discussion—, inversion cannot occur during hydrolysis of a steroid acetate (R = Me) to the free hydroxy-compound. A steroid alcohol and its acetate must therefore correspond in respect of the configuration of the substituent ·OH and ·OAc groups.

" β "-Cholestanyl chloride, m. p. 105° (Diels and Linn, *Ber.*, 1908, **41**, 260; Ruzicka, Goldberg, and Brungger, *Helv. Chim. Acta*, **1934**, **17**, 1389), reacts with acetate ions in *n*-valeric acid at 185° to furnish a product yielding by alkaline hydrolysis cholestan-3(β)-ol (II) (Marker, Whitmore, and Kamm, *J. Amer. Chem. Soc.*, **1935**, **57**, 2358), whilst " α "-cholestanyl chloride, m. p. 115° (Mauthner, *Monatsh.*, 1896, **17**, 579; Windaus and Hossfeld, *Z. physiol. Chem.*, 1925, **145**, 177; Ruzicka, Goldberg, and Wirz, *Helv. Chim. Acta*, 1935, **18**, 998), similarly affords cholestan-3(α)-ol (Marker, Whitmore, and Kamm, *loc. cit.*); a result analogous to that last named has also been reported by Marker *et al.* (*J. Amer. Chem. Soc.*, 1936, **58**, 338) for the cholestanyl bromide of m. p. 115°. These results have been confirmed and extended; treatment of " α "-cholestanyl chloride as described by Marker *et al.* leads to the isolation of 3(α)-hydroxycholestane (*epi*cholestanol), m. p. 183—185°, which was identified directly and by conversion into the acetate, m. p. 94—95°. The main product of the reaction, also isolated by direct crystallisation, is an unsaturated hydrocarbon, m. p. 70—72°, $[\alpha]_D^{20°}$ +63°±1°, which is probably identical with $\Delta^2$-cholestene, m. p. 69°, $[\alpha]_D^{20°}$ +64°, obtained by Mauthner (*Monatsh.*, 1909, **30**, 642) from the chloride by the action of hot quinoline and termed *neo*cholestene by him; [cf. also Blunschy, Hardegger, and Simon (*Helv. Chim. Acta*, 1946, **29**, 199), m. p. 73—74°, $[\alpha]_D$ +67°; Hattori and Kawasaki (*J. Pharm. Soc. Japan*, 1937, **57**, 115), m. p. 75°, $[\alpha]_D^{24°}$ +64°]; the production of $\Delta^3$-cholestene is, however, not excluded. The formation of $\Delta^2$- and/or $\Delta^3$-cholestene is not unexpected since Hughes, Ingold, and Scott (*J.*, 1937, 1271) have shown that an alkyl halide in a non-aqueous solvent and in the absence of a basic reagent can afford an olefin by a unimolecular mechanism (*E*1):



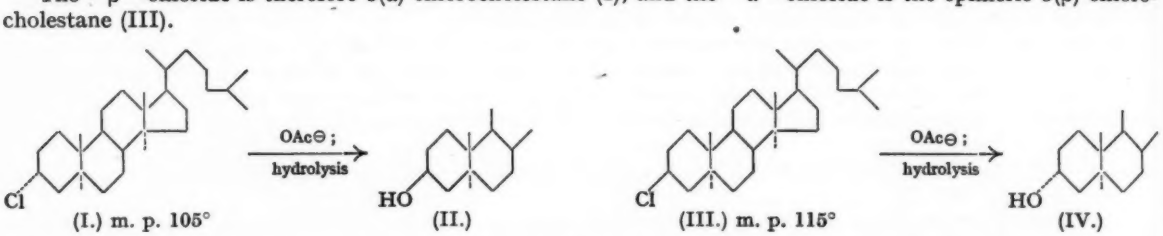

dependent on a slow halogen-ionisation, which is also the initial stage of the substitution mechanism $S_N1$, followed by rapid loss of a proton from the intermediate cation. From the present point of view, the process furnishing $\Delta^2$-cholestene simply puts some of the original chloride out of action; a quantitative investigation of the reaction product from " α "-cholestanyl chloride (250 mg.) was therefore undertaken. Chromatographic analysis gave $\Delta^2$-cholestene (167 mg.), 3(α)-hydroxycholestane (39 mg.), and 3(β)-hydroxycholestane (7 mg.). The elimination reaction therefore involved 73% of the original chloride, and the cholestanols isolated in pure crystalline condition represent a yield of 72% on the residual 27% of chloride. The relative proportions of the cholestanols isolated are 85% of the 3(α)- and 15% of the 3(β)-epimeride.

Similarly, a quantitative investigation of the colourless reaction product obtained by treatment of " β "-cholestanyl chloride (250 mg.) under the conditions prescribed by Marker *et al.* gave $\Delta^2$-cholestene (176 mg.), 3(α)-hydroxycholestane (5·5 mg.), and 3(β)-hydroxycholestane (40·5 mg.); the last two were identified directly and by conversion into the acetates. The elimination reaction here involved 77% of the chloride, whilst the cholestanols isolated in pure crystalline condition correspond to a yield of 84% on the residual 23% of chloride. The relative proportions of the cholestanols isolated are 12% of the 3(α)- and 88% of the 3(β)-epimeride.

The production of *both* epimerides in both experiments, but in markedly unequal and inverse proportions, is in accord with theoretical expectation. A bimolecular acetolysis (mechanism $S_N2$) should proceed with inversion and practically complete absence of racemisation, whilst a unimolecular acetolysis (mechanism $S_N1$) should take place with predominating inversion but with some racemisation (cf. Hughes, Ingold, and Masterman, *J.*, 1937, 1196). The following table summarises the results and suggests that the substitution mechanisms $S_N1$ and $S_N2$ operate side by side, and that if racemisation is confined essentially to mechanism $S_N1$ then that mechanism operates to the extent of some 24—30%.

| | Chloride involved in elimination reaction *E*1 (%). | Chloride involved in substitution reactions $S_N1$, $S_N2$ (%). | *epi*Cholestanol isolated (%). | Cholestanol isolated (%). |
|---|---|---|---|---|
| " α "-Cholestanyl chloride, m. p. 115°... | 74 | 26 | 70 ($S_N2$) + 15 ($S_N1$) | 15 ($S_N1$) |
| " β "-Cholestanyl chloride, m. p. 105°... | 77 | 23 | 12 ($S_N1$) | 76 ($S_N2$) + 12 ($S_N1$) |

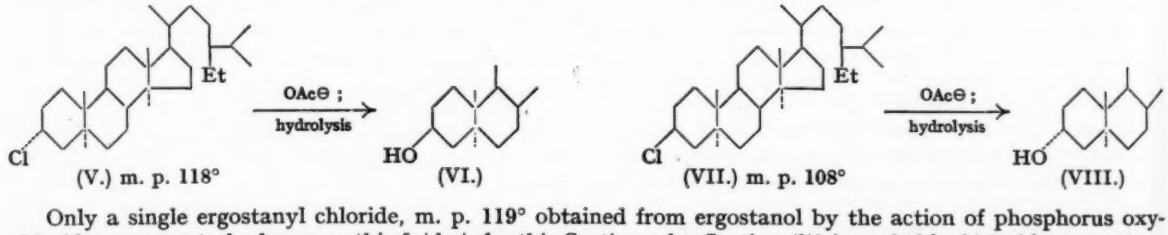
The " β "-chloride is therefore 3(α)-chlorocholestane (I), and the " α "-chloride is the epimeric 3(β)-chlorocholestane (III).




(I.) m. p. 105° (II.) (III.) m. p. 115° (IV.)

The configurations now assigned reverse the provisional trivial indices previously used for differentiation, and also reverse the stereochemical allocation suggested by Fieser (" The Chemistry of Natural Products Related to Phenanthrene," 2nd Edition, New York, 1937, pp. 392, 393) and by Barr, Heilbron, and Spring (*J.*, 1936, 737) on the basis of the rule that the m. p. of a *cis*($C_3/C_5$)-compound is higher than that of its *trans*-($C_3/C_5$)-isomeride, but are in harmony with the fortuitous allocation made by Sobotka (" The Chemistry of the Sterids," London, 1938, p. 61).

A similar situation exists in regard to the stigmastanyl chlorides; the so-called " β "-stigmastanyl chloride, m. p. 118°, reacts with acetate ions in *n*-valeric acid at 180° to furnish, after alkaline hydrolysis, stigmastanol (VI) (Marker and Lawson, *J. Amer. Chem. Soc.*, 1937, **59**, 2711); this chloride is therefore 3(α)-chlorostigmastane (V). Likewise, the so-called " α "-stigmastanyl chloride, m. p. 108°, affords *epi*stigmastanol (VIII) (Marker and Lawson, *loc. cit.*) and is therefore 3(β)-chlorostigmastane (VII).




(V.) m. p. 118° (VI.) (VII.) m. p. 108° (VIII.)

Only a single ergostanyl chloride, m. p. 119° obtained from ergostanol by the action of phosphorus oxychloride, appears to be known; this [*vide infra* this Section, also Section (*b*)] is probably 3(α)-chloroergostane and should furnish ergostanol by treatment with acetate ions and subsequent alkaline hydrolysis.

For saturated compounds, in which effects arising from " vicinal action " (Barton, *J.*, 1945, 813; this vol., p. 372) are excluded, molecular rotation differences, where available, can contribute supplementary evidence of configuration, and, as will be seen from Table I, these are in agreement with the configurations now assigned.

From the configurations thus assigned to (I) and (III), it follows that the " β "-chloroandrosterone, m. p. 128°, which results from (I) by oxidation with chromium trioxide (Ruzicka, Goldberg, and Brungger, *Helv. Chim. Acta*, 1934, **17**, 1389) is 3(α)-chloroandrostan-17-one (IX). It would appear not unreasonable to consider that the polar influence of the carbonyl group at $C_{17}$ upon the halogen at $C_3$ is extremely small, and to regard (IX) in respect of substitution reactions at $C_3$ as a secondary alkyl halide analogous to (I) and (III).

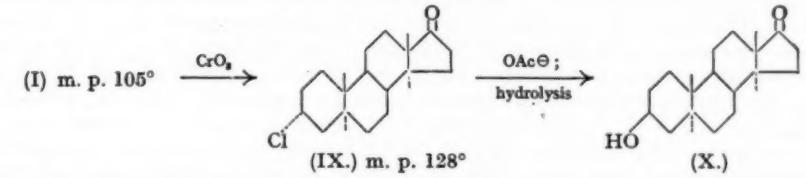
TABLE I.

(All rotations in chloroform at ~20°.)

| Substance. | 3(α). $[\alpha]_D$. | 3(α). $[M]_D$. | 3(β). $[\alpha]_D$. | 3(β). $[M]_D$. | $\Delta[M]_D$. |
|---|---|---|---|---|---|
| 3-Chlorocholestane | +30·5° [1] | +124° | +27° [1] | +110° | +14° |
| 3-Chlorostigmastane | — | — | — | — | — |
| 3-Hydroxycholestane | +26 [2] | +100 | +23 [3] | + 89 | +11 |
| 3-Hydroxystigmastane | +24 [4] | +108 | +24 [5, 6, 7] | +100 | + 8 |
| 3-Acetoxycholestane | +30 [1] | +129 | +14 [3] | + 60 | +69 |
| 3-Acetoxystigmastane | +28 [4] | +128 | +15 [5, 6, 7] | + 69 | +59 |

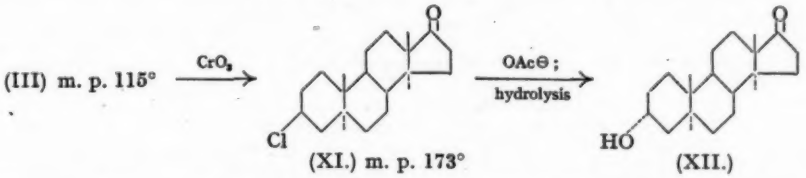
[1] This paper; Mauthner (*Monatsh.*, 1909, **30**, 635) gives $[\alpha]_D^{20°}$ +29·5° (*c*, 3·138 in chloroform) for the 3(β)-chlorocholestane. [2] Linstead, *J. Amer. Chem. Soc.*, 1940, **62**, 1766. [3] Barton, private communication. [4] Barton, *J.*, 1945, 813. [5] Dalmer *et al.*, *Ber.*, 1935, **68**, 1814. [6] Dischert, *Z. physiol. Chem.*, 1935, **237**, 32. [7] Coffey, Heilbron, and Spring, *J.*, 1936, 738.

On this assumption, reaction with acetate ions should and does proceed with substantially complete inversion to give *iso*androsterone acetate and, after hydrolysis, *iso*androsterone (X); here also incursion of the elimination reaction *E*1 (cf. p. 1141) leads to the production of $\Delta^2$- or $\Delta^3$-androsten-17-one. Incidentally, the chloro-*allo*cholanic acid, m. p. 195°, obtained as by-product in the oxidation of (I) (compare Barr, Heilbron, and Spring, *J.*, 1936, 737) must be 3(α)-chloro*allo*cholanic acid, and the lower homologue, m. p. 213° derived from it must be 3(α)-chloronor*allo*cholanic acid. This nor*allo*-acid, characterised as the methyl ester, m. p. 158°, was also obtained by Heilbron, Samant, and Simpson (*J.*, 1933, 1410) from ergostanyl chloride, m. p. 119°, by oxidation with chromium trioxide, and the constitution now assigned to it is consistent with the formulation (*vide supra*) of the chloride, m. p. 119°, as 3(α)-chloroergostane.




(IX.) m. p. 128° (X.)

Similarly, the " α "-chloroandrosterone, m. p. 173°, which is obtained from (III) by oxidation with chromium trioxide (Ruzicka, Wirz, and Meyer, *Helv. Chim. Acta*, 1935, **18**, 998; Marker, Whitmore, and Kamm, *J. Amer. Chem. Soc.*, 1935, **57**, 2358) is 3(β)-chloroandrostan-17-one (XI), which by treatment with acetate ions in acetic acid undergoes inversion to afford androsterone acetate and, after hydrolysis, androsterone (XII) (Butenandt and Dannenbaum, *Z. physiol. Chem.*, 1934, **229**, 192; Ruzicka, Wirz, and Meyer, *loc. cit.*; Marker, Whitmore, Kamm, Oakwood, and Blattermann, *J. Amer. Chem. Soc.*, 1936, **58**, 338); Butenandt and Dannenbaum record the formation of $\Delta^3$-androsten-17-one, which again clearly arises from the inclusion of the elimin-




(XI.) m. p. 173° (XII.)

ation reaction *E*1. The acid, m. p. 175° (compare Windaus and Hossfeld, *Z. physiol. Chem.*, 1935, **145**, 177), accompanying (XI) must be 3(β)-chloro*allo*cholanic acid, and its lower homologues, m. p. 238° (Heilbron, Samant, and Spring, *loc. cit.*), and m. p. 231° (Marker *et al.*, *J. Amer. Chem. Soc.*, 1937, **59**, 768), must be correspondingly 3(β)-chloronor- and 3(β)-chlorobisnor-*allo*cholanic acid; the latter has been degraded to a 20-ketone which must be 3(β)-chloro*allo*pregnan-20-one and which reacts with acetate ions with inversion of configuration to give 3(α)-hydroxy*allo*pregnan-20-one.

The molecular rotation differences are given in Table II, and support the configurations now assigned to the 3-chloroandrostan-17-ones.

In this case further supporting evidence can be supplied by physiological activity, which is known to be extremely susceptible to minor structural modification. *iso*Androsterone (X) is some ten times less active in the comb-growth test than androsterone (XII), *i.e.*, a 3(β)-substituent appears to depress androgenic activity as compared with the same 3(α)-substituent. On the basis of the configurations now assigned, it would therefore be expected that (IX) should exhibit greater androgenic activity than (XI). This is so; Ruzicka, Wirz, and Meyer (*Helv. Chim. Acta*, 1935, **18**, 998) have reported that (XI) is at least four times less active than (IX) in the comb-growth test.

(*b*) *Replacement of* OR *by* Cl *with* $PCl_5$ *and* $SOCl_2$.—The conversion of alcohols into alkyl halides was discussed by Cowdrey, Hughes, Ingold, Masterman, and Scott (*loc. cit.*) and has recently been summarised by

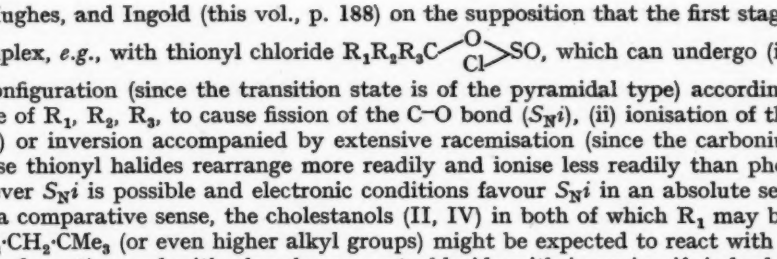
TABLE II.

(Rotations in chloroform at ~20°.)

| Substance. | 3(α). $[\alpha]_D$. | 3(α). $[M]_D$. | 3(β). $[\alpha]_D$. | 3(β). $[M]_D$. | $\Delta[M]_D$. |
|---|---|---|---|---|---|
| 3-Chloroandrostane-17-one | +94° [1] | +290° | +92° [1] | +284° | + 6° |
| 3-Hydroxyandrostane | + 2 [2] | + 6 | + 1 [2] | + 3 | + 3 |
| 3-Hydroxy-$\Delta^{16}$-androstene | +14 [2] | + 38 | +11 [2] | + 30 | + 8 |
| 3-Hydroxyandrostan-17-one | +88 [3] | +255 | +81 [3] | +235 | +20 |
| | +96 [4] | +278 | +94 [5] | +273 | + 5 |
| | — | — | +90 [6] | +261 | — |
| 3-Acetoxyandrostan-17-one | +77 [3] | +256 | +65 [3] | +216 | +40 |
| | +86 [7] | +286 | +76 [5] | +252 | +34 |
| | — | — | +69 [6] | +229 | — |

[1] This paper. [2] Prelog, Ruzicka, and Wieland, *Helv. Chim. Acta*, 1944, **27**, 1164. [3] Reichstein and von Euw, *ibid.*, 1942, **25**, 988, determined in dioxan. [4] Butenandt and Tscherning, *Z. physiol. Chem.*, 1934, **229**, 167; David *et al.*, *ibid.*, 1935, **233**, 281; Discherl, *ibid.*, 1935, **237**, 52; Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1389, 1395; Hirschmann, *J. Biol. Chem.*, 1940, **136**, 483, all in EtOH. [5] Barton, private communication, determined in EtOH. [6] Barton, private communication. [7] Butenandt and Dannenbaum, *Z. physiol. Chem.*, 1934, **229**, 192, determined in EtOH.

Dostrovsky, Hughes, and Ingold (this vol., p. 188) on the supposition that the first stage is always the formation of a complex, *e.g.*, with thionyl chloride $R_1R_2R_3C\text{—}O\text{—}\overset{Cl}{}>SO$, which can undergo (i) rearrangement with retention of configuration (since the transition state is of the pyramidal type) according to the capacity for electron release of $R_1$, $R_2$, $R_3$, to cause fission of the C—O bond ($S_Ni$), (ii) ionisation of the halogen atom with inversion ($S_N2$) or inversion accompanied by extensive racemisation (since the carbonium ion is nearly flat) ($S_N1$). Because thionyl halides rearrange more readily and ionise less readily than phosphorus halides, and because whenever $S_Ni$ is possible and electronic conditions favour $S_Ni$ in an absolute sense, $S_N1$ and $S_N2$ are superseded in a comparative sense, the cholestanols (II, IV) in both of which $R_1$ may be regarded as $CHMe_2$ and $R_2$ as $CH_2{\cdot}CH_2{\cdot}CMe_3$ (or even higher alkyl groups) might be expected to react with thionyl chloride with retention of configuration and with phosphorus pentachloride with inversion if, indeed, they afford different products with these reagents. This is in fact so; cholestan-3(α)-ol (IV) reacts with thionyl chloride (Marker, Whitmore, and Kamm, *J. Amer. Chem. Soc.*, 1935, **57**, 2358) to yield 3(α)-chlorocholestane (I) and with phosphorus pentachloride (Marker, Whitmore, and Kamm, *loc. cit.*) or phosphorus tribromide (Ruzicka, Wirz, and Meyer, *Helv. Chim. Acta*, 1935, **18**, 998; Marker *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 340) to give 3(β)-chloro(bromo)cholestane (III); similarly, cholestan-3(β)-ol (II) reacts with thionyl chloride (Marker, Kamm, and Whitmore, *loc. cit.*) to furnish 3(β)-chlorocholestane (III), and with phosphorus pentachloride (Diels and Linn, *Ber.*, 1908, **41**, 260; Windaus, *ibid.*, 1917, **50**, 133; cf. Ruzicka, Goldberg, Brungger, *Helv. Chim. Acta*, 1934, **17**, 1392) to afford 3(α)-chlorocholestane (I).

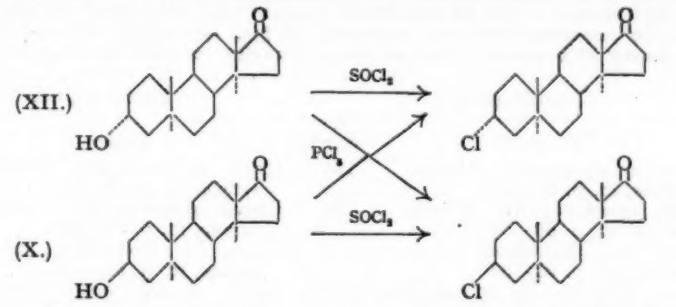



No evidence is available as to occurrence of racemisation in these reactions, but the resulting configurational relationships are in harmony with those established in section (*a*). The use of hydrochloric acid as the substituting reagent should cause inversion and furnish the same products as are obtained with phosphorus pentachloride.

A similar situation exists in respect of the stigmastanols; stigmastan-3(α)-ol (VIII) with thionyl chloride gives 3(α)-chlorostigmastane, m. p. 118° (V), and with phosphorus pentachloride yields 3(β)-chlorostigmastane, m. p. 108° (VII), whilst stigmastan-3(β)-ol (VI) furnishes 3(β)-chlorostigmastane (VII) with thionyl chloride and 3(α)-chlorostigmastane (V) with phosphorus pentachloride (Marker and Lawson, *J. Amer. Chem. Soc.*, 1937, **59**, 2711).

Assuming once again that the polar influence at $C_3$ of the carbonyl group at $C_{17}$ is very small, similar considerations should be applicable to the reactions of androsterone (XII) and *iso*androsterone (X) with thionyl chloride and phosphorus pentachloride. *iso*Androsterone (X) reacts with thionyl chloride to give 3(β)-chloroandrostan-17-one (XI) (Marker, Whitmore, Kamm, Oakwood, and Blatterman, *J. Amer. Chem. Soc.*, 1936, **58**, 338) with retention of configuration, whilst androsterone (XII) is now found similarly to furnish 3(α)-chloroandrostan-17-one (IX) but in traces, the principal product under all conditions used being a high-melting substance, probably androsterone sulphite. Use of 1 mol. of phosphorus pentachloride is found

to convert androsterone (XII) into 3(β)-chloroandrostan-17-one (XI) * and *iso*androsterone (X) into 3(α)-chloroandrostan-17-one (IX), in accordance with the theoretical expectation of inversion of configuration,




and in good yield.† Theory suggests that use of thionyl chloride in presence of pyridine may reverse the stereochemical course of reaction and lead to inversion of configuration.

It is proposed in the near future to examine the application of the considerations developed in the foregoing to derivatives of 6-ketocholestane, ætiocholane, *allo*cholane, cholane, and coprostane.

## Experimental.

(All m. ps. were thermo-electrically determined on a Kofler block and are therefore corrected; limit of error ±2°. All optical rotations were determined in chloroform.)

*3(α)-Chlorocholestane* (I).—3(β)-Hydroxycholestane (m. p. 139—140°, giving no colour with tetranitromethane; 165 mg.) was treated with phosphorus pentachloride (200 mg.) according to the directions of Ruzicka *et al.* (*Helv. Chim. Acta*, 1934, **17**, 1389); the product gave a faint but definite yellow colour with tetranitromethane, and was therefore dissolved in pure acetic acid (2 c.c.) and treated with a 2% solution of chromium trioxide in acetic acid (2·0 c.c. ≡ 1·5 atoms of oxygen) for 0·5 hour at 60°. After working up, the neutral product was dissolved in pentane and separated from neutral oxidation products by filtration through a column of aluminium oxide (Merck–Brockmann, activity III—IV; 0·5 g.) prepared in pentane. The product obtained by elution with pentane represented a yield of 90%; after recrystallisation from acetone, 3(α)-chlorocholestane was obtained as plates, m. p. 95° with partial transformation to prisms, m. p. 103—105°; $[\alpha]_D^{20°}$ +30·5°±1° (*c*, 1·377 in chloroform), giving no colour with tetranitromethane. A second preparation yielded prisms, m. p. 103—105°, the polymorphic plate-form not being observed.

*Acetolysis.* The chloride (I) (250 mg.), anhydrous potassium acetate (2·5 g.), and *n*-valeric acid (5 c.c.) were refluxed with exclusion of moisture for 30 hours. The product was completely colourless and was treated with 2N-sodium carbonate (25 c.c.) and extracted with ether. The extract was washed with 2N-sodium carbonate and then with water, dried ($Na_2SO_4$), and evaporated. The residue was hydrolysed with 4% methyl-alcoholic potassium hydroxide (2·5 c.c. ≡ *ca.* 3 mols.) for 2 hours; after addition of a few drops of water, saturation with carbon dioxide, and removal of methanol under reduced pressure, the product was extracted with ether. The ethereal extract was washed with a little water, dried ($Na_2SO_4$), and evaporated to give a colourless oil (231 mg.), which was dissolved in benzene (0·25 c.c.), diluted with a little pentane and introduced on to a column of aluminium oxide (Merck–Brockmann, activity III—IV; 7 g.) prepared in 25 c.c. of pentane. Using eluates of 25 c.c. the analysis of the product is shown in Chromatogram A. Fractions 1—3 were united and recrystallised from acetone to yield $\Delta^3$-cholestene, m. p. 69—70°, $[\alpha]_D^{20°}$ +64°±1° (*c*, 2·025 in chloroform); the upper layer remained colourless with chloroform–sulphuric acid, but developed an intense violet colour on addition of acetic anhydride. A solution of the hydrocarbon in ether–acetic acid, treated with the calculated amount of a solution of bromine in acetic acid, gave by evaporation under reduced pressure an oily dibromide, which crystallised partly when moistened with methanol and kept at 0°; the crystalline material was recrystallised from ethanol to give an impure dibromide, m. p. 100—104° (Mauthner, *loc. cit.*, gives m. p. 125°). Fractions 7 and 8 were united and recrystallised from ethanol to yield pure cholestane-3(α)-ol, m. p. 186—187°, mixed m. p. 186—187°; the crystals were boiled with acetic anhydride for 10 minutes, excess of the reagent was removed under reduced pressure, and the crystalline residue was recrystallised from methanol to yield needles of the acetate, m. p. 94—95°, mixed m. p. 94—96° with a genuine specimen. Fractions 11 and 12, consisting of pure cholestan-3(β)-ol, were identified by similar conversion into the acetate which, recrystallised from ethyl acetate–methanol, formed prisms, m. p. 109—110°, mixed m. p. 109—110°.

*3(β)-Chlorocholestane* (III).—Prepared by hydrogenation of cholesteryl chloride, and suitably purified (see Part II, following paper), the compound formed prisms, m. p. 114—115°, $[\alpha]_D^{20°}$ +27°±1° (*c*, 1·911 in chloroform).

*Acetolysis.* The chloride (III) (250 mg.), anhydrous potassium acetate (2·5 g.), and *n*-valeric acid (5 c.c.) were refluxed for 30 hours with exclusion of moisture. The product was somewhat discoloured and was isolated and hydrolysed as described above. The brown reaction product (230 mg.) was boiled with methanol in which it was not appreciably soluble and the clear colourless solution decanted from the undissolved material and allowed to crystallise. Two kinds of crystal were readily separated by hand-picking: (i) very long thin prisms, m. p. 70—72°, of $\Delta^3$-cholestene, (ii) compact prisms, m. p. 180—183°, of cholestan-3(α)-ol, mixed m. p. 181—185°, the melt recrystallising at 182° and remelting at 185°. The whole material was re-united, dissolved in benzene (0·25 c.c.), and introduced on to a column of aluminium oxide (Merck–Brockmann, activity III—IV, 7 gm.) prepared in pentane (25 c.c.); the details of the chromatographic analysis, using eluates of 25 c.c., are set out in chromatogram B. The $\Delta^3$-cholestene contained in fractions 1—3 was recrystallised from acetone to give prisms, m. p. 68—70°, $[\alpha]_D^{20°}$ +63°±1° (*c*, 2·015 in chloroform). Fractions 7, 8, and 9 were united and recrystallised from methanol to yield pure cholestan-3(α)-ol, m. p. 186—187°, mixed m. p. 186—187° (acetate, m. p. 94—95°, mixed m. p. 93—95°). Fractions 11 and 12 were united and recrystallised from methanol to give plates (7 mg.), m. p. *ca.* 125° with immediate recrystallisation as prisms, m. p. 141—142°; mixed m. p. determinations with pure cholestan-3(β)-ol showed a partial transition at *ca.* 125°, and melted finally at 141—142°; the material

* Since this experiment was carried out, it has been discovered that the conversion of androsterone (XII) into the chloride, m. p. 173°, now assigned the 3(β)-chloro-configuration (XI), by use of phosphorus pentachloride had already been achieved by Hirschmann (*J. Biol. Chem.*, 1940, **136**, 483).

† The apparent absence of racemisation in these reactions suggests that mechanism $S_N1$ is largely excluded.

gave a precipitate with digitonin in 90% methanol, and by acetylation yielded the acetate of cholestan-3(β)-ol, m. p. 109—110°, mixed m. p. 109—110°.

3(α)-*Chloroandrostan*-17-*one* (IX).—(a) *From* iso*androsterone*. *iso*Androsterone (m. p. 175—176°; 65 mg.), prepared by hydrolysis of a highly purified specimen of the acetate, double m. p. 97° and 102—104°, was dissolved in pure dry chloroform * (2·5 c.c.) at 0°, and dry precipitated calcium carbonate (65 mg.) was added, followed by phosphorus pentachloride (90 mg.) with stirring during 15 minutes. After addition of sodium bicarbonate solution (5 c.c.) and a

| | | Chromatogram A. | | Chromatogram B. | |
|---|---|---|---|---|---|
| No. | Eluant. | Eluate. | Wt. (mg.). | Eluate. | Wt. (mg.) |
| 1 | Pentane | Cryst. spontaneously, $\Delta^2$-cholestene, m. p. 67—69°. | 135·5 | Cryst. spontaneously, $\Delta^2$-cholestene, m. p. 67—68°. | 138 |
| 2 | „ | Cryst. spontaneously, $\Delta^2$-cholestene, m. p. 66—68°. | 36 | Cryst. spontaneously, $\Delta^2$-cholestene, m. p. 65—68°. | 25 |
| 3 | „ | Cryst. by inoculation, $\Delta^2$-cholestene, m. p. 65—66°. | 3 | Cryst. by inoculation, $\Delta^2$-cholestene, m. p. 64—67°. | 4 |
| 4 | „ | Cryst. partially by inoculation, $\Delta^2$-cholestene? | 1·5 | Trace of oil, cryst. partly by inoculation. | 1 |
| 5 | Benzene–pentane 1 : 4 | Oil. | 0·5 | Oil. | 1 |
| 6 | „ „ 1 : 1 | Oil. | 0·5 | Brown gum, could not be cryst. from methanol at 0°. | 5 |
| 7 | „ „ 1 : 1 | Cryst. spontaneously, cholestan-3(α)-ol, m. p. 182°, the melt recryst. at 178°. | 2 | Cryst. spontaneously, cholestan-3(α)-ol, m. p. 185°. | 27 |
| 8 | „ „ 1 : 1 | Cryst. spontaneously, cholestan-3(α)-ol, m. p. 185°, the melt recryst. at 182°. | 3·5 | Cryst. spontaneously, cholestan-3(α)-ol, m. p. 183—185°. | 5 |
| 9 | „ „ 1 : 1 | | — | Cryst. spontaneously, cholestan-3(α)-ol, m. p. 182—183°. | 1 |
| 10 | Benzene | Partly crystalline. | 1 | Crystalline but coloured cholestan-3(α)-ol, m. p. 178—182°. | 6 |
| 11, 12 | Ether. | Cryst. spontaneously, m. p. 139—141° with recryst. of the melt at 140°; cholestan-3(β)-ol. | 40·5 | Cryst. spontaneously, m. p. 135—140°, largely cholestan-3(β)-ol. | 11·5 |
| 13 | Ether | | — | Trace of cryst. material. | 0·5 |
| | | Total | 224 | Total | 225 |

sufficient quantity of ether, the aqueous layer was separated, acidified with 2N-hydrochloric acid, and re-extracted with ether. The united extracts were washed with 2N-hydrochloric acid, 2N-sodium carbonate, and water, dried ($Na_2SO_4$), and evaporated. The product was taken up in sufficient boiling light petroleum (b. p. 80—100°), from which unchanged *iso*androsterone, m. p. 175° (38 mg.) separated on cooling. This material was retreated with phosphorus pentachloride (55 mg.), and the product was combined with the residue of reduced-pressure evaporation of the above light petroleum mother liquor and introduced on to a column of aluminium oxide (Merck–Brockmann, activity III—IV; 2 g.) prepared in pentane. Elution with benzene–pentane (1 : 4, 2 × 10 c.c. and 1 : 2, 10 c.c.) gave fractions which crystallised spontaneously after complete evaporation; further elution with benzene–pentane (1 : 2) gave only traces of material which failed to crystallise by seeding. The crystalline fractions were united and the product recrystallised from methanol to yield 3(α)-chloroandrostan-17-one (26 mg.) in characteristic stout prisms, m. p. 128°, mixed m. p. 128°. Elution of the column with dry ether (2 × 10 c.c.) yielded *iso*androsterone, m. p. 175° (28 mg.); allowance being made for this recovered material, the yield of chloride was 67%.

(b) *From androsterone*. (i) Androsterone (50 mg.) was dissolved in dry ether (2 c.c.), dry precipitated calcium carbonate (50 mg.) added, and pure redistilled thionyl chloride (1 c.c.) added dropwise with stirring at 15° during 0·5 hour. After 4 hours at room temperature, the mixture was completely evaporated under reduced pressure, and the product extracted with chloroform–ether (cf. Butenandt and Dannenbaum, *Z. physiol. Chem.*, 1934, **229**, 192). The material so obtained was chromatographed over aluminium oxide, but elution with benzene–pentane (1 : 4 and 1 : 2) gave only insignificant amounts of oil. Elution with benzene and benzene–ether mixtures yielded a substance, insoluble in methanol, which tended to separate as a jelly on concentration of the solution. The substance could not be crystallised satisfactorily, but was obtained crystalline by complete evaporation of a benzene solution and moistening of the residual oil with acetone; m. p. 200° (approx.); since hydrolysis with 4%-methyl-alcoholic potassium hydroxide in the presence of a little benzene furnished an almost quantitative yield of androsterone, the substance is regarded as androsterone sulphite.

(ii) Since under appropriate conditions cholesterol reacts with thionyl chloride to give cholesterol sulphite (Daughensbaugh and Allison, *J. Amer. Chem. Soc.*, 1929, **51**, 3665) and since the writer has found 3(β)-hydroxycholestane similarly to afford a quantitative yield of the *sulphite* [iridescent plates, m. p. 194°, from much hot acetone (Found: C, 79·12; H, 11·39. $C_{54}H_{94}O_3S$ requires C, 78·78; H, 11·50%)], the order of addition was reversed so that excess of thionyl chloride was always present. To a solution of thionyl chloride (2 c.c.) in dry ether (2 c.c.) containing dry calcium carbonate (100 mg.), a solution of androsterone (35 mg.) in dry ether (5 c.c.) was added dropwise at 5° during 0·25 hour. After being left for 4 hours to attain room temperature, the mixture was worked up as above, and chromatographed on aluminium oxide (Merck–Brockmann, 1 g.). Elution with benzene–pentane (1 : 4) yielded 3(α)-chloroandrostan-17-one (2 mg.), m. p. 123—125°, which did not depress the m. p. of a genuine specimen. Elution with benzene and benzene–ether mixtures yielded androsterone sulphite, which again formed the principal product of the reaction. Lack of material precluded a search for more favourable conditions.

For determination of the specific rotation, a genuine but slightly discoloured specimen, m. p. 125·5°, prepared by oxidative degradation of 3(α)-chlorocholestane and supplied by Professor Ruzicka, was purified chromatographically (*vide supra*); the product after recrystallisation from methanol formed stout colourless prisms, m. p. 128°, $[\alpha]_D^{22°}$ +94° ± 1·5° (*c*, 1·695).

* "AnalaR" chloroform was shaken for 24 hours with excess of calcium chloride, filtered, distilled, and used immediately.

3(β)-*Chloroandrostan*-17-*one* (XI).—Androsterone, m. p. 182° (54 mg.) was dissolved in chloroform at 0°, and treated with phosphorus pentachloride (80 mg.) in the presence of calcium carbonate (55 mg.) (*vide supra*). Working up yielded a product which, taken up in light petroleum (b. p. 80—100°), yielded unaltered androsterone, m. p. 180—182° (36 mg.). This material was retreated with phosphorus pentachloride (50 mg.) and the product together with the residue obtained by evaporation of the light petroleum mother-liquor submitted to chromatographic analysis on aluminium oxide; elution with benzene–pentane (1 : 4) gave fractions which crystallised spontaneously and which, united and recrystallised from ethanol, yielded 3(β)-chloroandrostan-17-one as needles, m. p. 172—173° (16 mg.), $[\alpha]_D^{20°}$ +92°±2° (*c*, 1·400) (Found: C, 74·0; H, 9·7. Calc. for $C_{19}H_{29}OCl$: C, 73·9; H, 9·5%). A first elution of the column with benzene–pentane (1 : 2) (10 c.c.) gave a mere trace of material and a second similar elution gave nothing; subsequent elution with dry ether (2 × 10 c.c.) afforded unchanged androsterone, m. p. 179—182° (32 mg.). Allowance being made for this recovered androsterone, the yield of chloride was 70%.

iso*Androsterone Acetate from* 3(α)-*Chloroandrostan*-17-*one* (IX).—The chloride (20 mg., m. p. 128°) was heated for 2 hours at 180° (aniline-vapour bath) with a 20% solution of fused potassium acetate in pure acetic acid in a small bomb-tube. After cooling, the contents of the tube were poured into water, and the product extracted with ether–chloroform; the extract was washed with water, sodium carbonate solution, and again with water, dried ($Na_2SO_4$), and evaporated. The residue (18 mg.) was partly crystalline and was introduced by a minimum of benzene on to a column of aluminium oxide (Merck–Brockmann, 0·6 g.) prepared in pentane. Elution with pentane and benzene–pentane mixtures (1 : 9, 1 : 4) gave fractions which crystallised spontaneously; these were united after appropriate examination and recrystallised from methanol to yield rectangular plates, m. p. 105°, of $\Delta^2$ (or $\Delta^{3(2)}$)-androsten-17-one (Found: C, 80·0; H, 10·5. Calc. for $C_{19}H_{28}O$: C, 80·2; H, 10·3%) (cf. Marker, Kamm, Jones, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1363; Hirschmann, *J. Biol. Chem.*, 1940, **136**, 483; Venning, Hoffman, and Browne, *ibid.*, 1942, **146**, 369). Elution with benzene–pentane (1 : 1) gave a fraction which, recrystallised from dilute methanol, yielded *iso*androsterone acetate (4 mg.) as leaflets, m. p. 96—97°, with partial recrystallisation and remelting at 101—103°, which did not depress the m. p. of a genuine specimen. Subsequent elution with benzene–ether mixtures gave only traces of oil which failed to crystallise.

The author wishes gratefully to acknowledge gifts of the following specimens: 3(α)-hydroxycholestane from Dr. R. P. Linstead, 3(β)-hydroxycholestane from Dr. P. G. Marshall of British Drug Houses Ltd., 3(α)-acetoxycholestane from Sir Ian Heilbron, 3(α)-chloroandrostan-17-one and androsterone from Professor L. Ruzicka, and *iso*androsterone acetate from Professor T. Reichstein; and also the support of the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund, and the Anna Fuller Fund.

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[*Received, August 8th*, 1946.]

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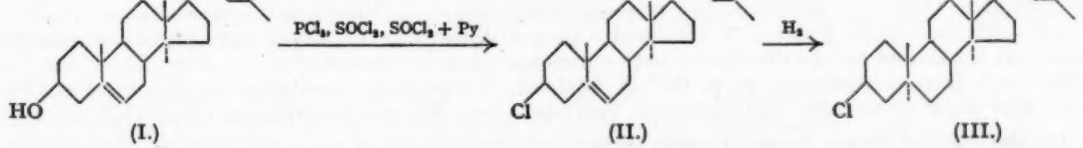
## 254. *Steroids and the Walden Inversion. Part II. Derivatives of Δ⁵-Cholestene and Δ⁵-Androstene.*

By C. W. SHOPPEE.

On the basis of the constitutions assigned in Part I, cholesteryl chloride is shown to be 3(β)-chloro-Δ⁵-cholestene. The steric orientation of substitution reactions at $C_3$ in Δ⁵-steroids is discussed; in striking contrast to the general occurrence of inversion in the replacement reaction ·Cl ⟶ ·OR and the occurrence of inversion or retention according to the orientation rules of Cowdrey *et al.* (*J.*, 1937, 1252) for the substitution ·OR ⟶ ·Cl in the saturated series, both these types of replacement take place in the Δ⁵-series with preservation of configuration and irrespective of the substituting agent within the range of reagents and conditions examined. It is suggested that the retention of configuration characteristic of the substitution reactions at $C_3$ of Δ⁵-steroids is due to polarisation of the $C_5$:$C_6$-double bond, the electrons of which interact with the cationic charge formed at $C_3$ by ionisation of the group substituted to produce a $C_3$–$C_5$ bond of mixed covalent–electrovalent type; this binding leads to a pyramidal configuration for the transition state and so to preservation of configuration.

On this basis, a consistent picture is obtained for substitution reactions at $C_3$ in the Δ⁵-steroid series, which harmonises with the configurations assigned (Part I) in the saturated series.

IN Part I (preceding paper), arguments were adduced to show that the so-called " α "-cholestanyl chloride, m. p. 115°, has the constitution 3(β)-chlorocholestane (III). When cholesterol (I) is treated with phosphorus pentachloride (Planer, *Annalen*, 1861, **118**, 25; Loebisch, *Ber.*, 1872, **3**, 510; Mauthner, *Monatsh.*, 1894, **15**, 87), or with thionyl chloride alone (Diels, Abderhalden, and Blumberg, *Ber.*, 1904, **37**, 3092; 1911, **44**, 287) or in presence of pyridine (Daughensbaugh and Allison, *J. Amer. Chem. Soc.*, 1929, **51**, 3665), high yields of one and the same product, cholesteryl chloride, m. p. 96°, are obtained. Since catalytic hydrogenation of cholesteryl chloride affords 3(β)-chlorocholestane (III) (Mauthner, *Monatsh.*, 1909, **30**, 635; Marker, Whitmore, and Kamm, *J. Amer. Chem. Soc.*, 1935, **57**, 2358) in quantitative yield (*vide infra*), cholesteryl chloride is to be regarded as 3(β)-chloro-Δ⁵-cholestene (II). Crystallographic evidence also supports this view: " from

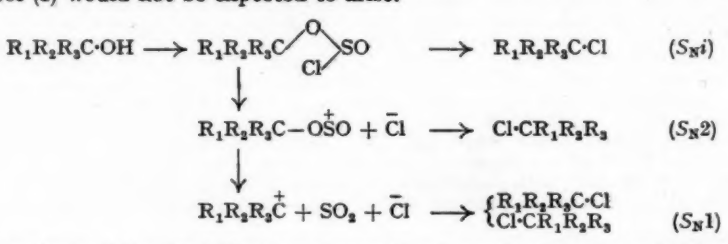



(I.) (II.) (III.)

the crystal unit cell dimensions and even more from the intensities of the *c* plane reflexions, it is clear that " α "-cholestanyl chloride has the same configuration (at $C_3$) as cholesteryl chloride " (Crowfoot, " Vitamins

and Hormones," New York, 1944, Vol. 2, p. 450). The hydroxyl group of cholesterol thus consistently undergoes replacement by chlorine with retention of configuration.

This relationship is unusual, inasmuch as although the three reagents specified can yield the same stereochemical product (*e.g.*, with β-*n*-octyl alcohol, ethyl lactate), they then cause inversion (mechanisms $S_N1$, $S_N2$). Retention of configuration according to the concepts laid down by Ingold *et al.* (*J.*, 1937, 1252) and recently summarised by Dostrovsky, Hughes, and Ingold (this vol., p. 186 *et seq.*) requires an intramolecular mechanism ($S_Ni$), leading to a transition state of pyramidal type, which is promoted by electron releasing groups and under conditions inhibitory to ionisation; retention of configuration with employment of all the three reagents specified is rational only if the structural influences favour mechanism $S_Ni$ sufficiently, and would be the logical outcome of very powerful electron release—a circumstance which from inspection of the formula of cholesterol (I) would not be expected to arise.

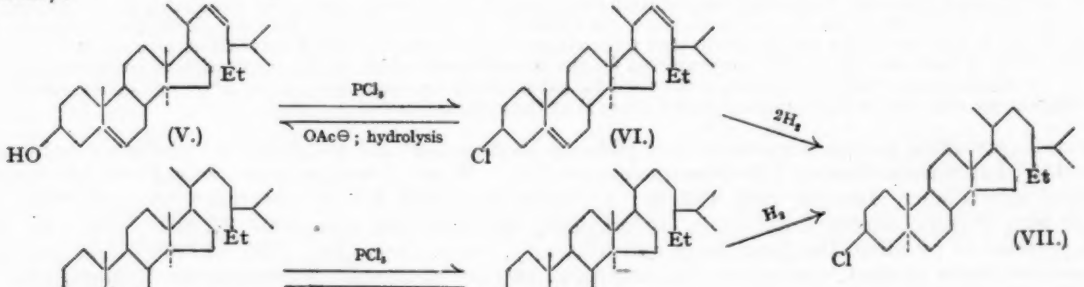


This singular behaviour of the $\Delta^5$-cholestene system is not confined to the substitution of OR by Cl, but also appears in the replacement of Cl by OR. When cholesteryl chloride (II) is treated with acetate ions in acetic acid at 100°, the product is almost pure cholesteryl acetate (IV) (cf. Bergmann, *J. Amer. Chem. Soc.*, 1938, **60**, 1996), and hydrolysis furnishes a 91% overall yield of cholesterol * (I), unaccompanied by *epi*-cholesterol:

$$\text{(II)} \xrightarrow{\text{OAc}\ominus} \text{(IV; = II with OAc for Cl)} \xrightarrow{\text{OH}\ominus} \text{(I)}$$

Thus here substitution occurs with apparently complete retention of configuration, and in sharp contrast with the corresponding substitution reactions of the cholestanyl chlorides, and secondary alkyl halides generally, which proceed (mechanisms $S_N1$, $S_N2$) with substantially complete inversion of configuration; and it is difficult to envisage the operation of some internal rearrangement mechanism analogous to $S_Ni$ in an essentially ionic reaction such as the conversion of (II) to (IV) by acetate ions in an ionising medium.

A similar situation exists in the relations subsisting between other $\Delta^5$-sterols and their 3-chloro-derivatives. Thus stigmasterol (V) by treatment with phosphorus pentachloride undergoes substitution with retention of configuration to furnish stigmasteryl chloride, which must possess the 3(β)-chloro-constitution (VI) because catalytic hydrogenation affords 3(β)-chlorostigmastane [3(β)-chlorositostane] (VII) (cf. Part I, *loc. cit.*). Treatment of stigmasteryl chloride (V) with acetate ions in acetic acid at 100°, with subsequent alkaline hydrolysis, regenerates stigmasterol (IV) with retention of configuration (Marker and Lawson, *J. Amer. Chem. Soc.*, 1937, **59**, 2711):



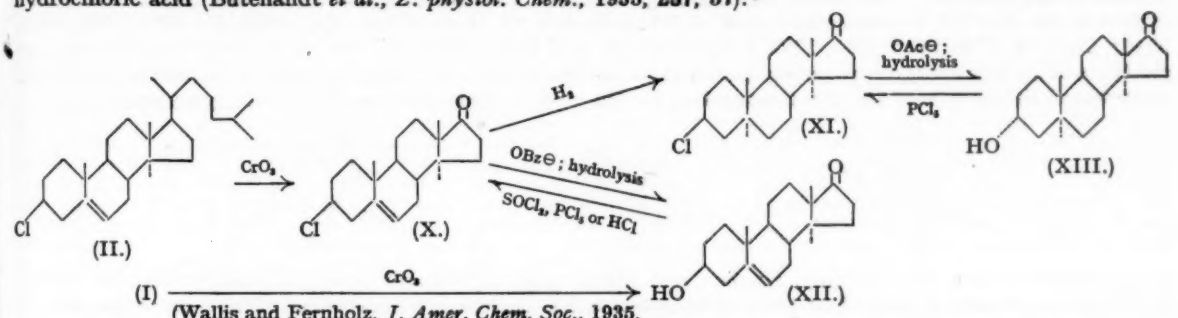

Likewise " β "-sitosterol (VIII) reacts with phosphorus pentachloride to yield " β "-sitosteryl chloride (IX) with retention of configuration, since catalytic hydrogenation of the last-named substance affords 3(β)-chlorostigmastane (VII); whilst treatment of (IX) with acetate ions in acetic acid at 100° and subsequent alkaline hydrolysis regenerates " β "-sitosterol with retention of configuration (Marker and Lawson, *loc. cit.*).

Once again, a similar position is disclosed amongst derivatives of $\Delta^5$-androstene. When cholesteryl chloride (II) is oxidised (as the dibromide) with chromium trioxide (Marker *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 338) " α "-chloroandrostenone, m. p. 157°, is obtained; this must be regarded as 3(β)-chloro-$\Delta^5$-androsten-17-one (X),† since (i) catalytic hydrogenation converts it into 3(β)-chloroandrostan-17-one (XI) (cf. Part I,

* The statement of Marker, Kamm, Fleming, Popkin, and Wittle (*J. Amer. Chem. Soc.*, 1937, **59**, 619) which is not supported by experimental evidence is thus confirmed.

† This compound has no androgenic activity in the comb test (Ruzicka, Goldberg, and Wirz, *Helv. Chim. Acta*, 1935, **18**, 998).

*loc. cit.*) and (ii) it is obtained from 3(β)-hydroxy-Δ⁵-androsten-17-one (dehydro*iso*androsterone) (XII) not only by treatment with thionyl chloride—a reagent which tends to substitute with retention of configuration—but also by use of phosphorus pentachloride (Wallis and Fernholz, *J. Amer. Chem. Soc.*, 1937, **59**, 764) and of hydrochloric acid (Butenandt *et al.*, *Z. physiol. Chem.*, 1935, **237**, 57).*



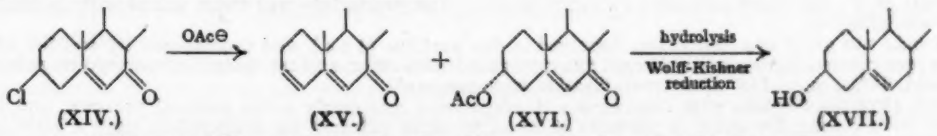

(Wallis and Fernholz, *J. Amer. Chem. Soc.*, 1935, **57**, 1504; Marker *et al.*, *ibid.*, 1936, **58**, 338).

In striking contrast to the reaction of (XI) with acetate ions in acetic acid, which proceeds with inversion to yield androsterone acetate and, after hydrolysis, androsterone (XIII)—a reaction which can be reversed by use of phosphorus pentachloride, a reagent which tends to substitute with inversion of configuration—3(β)-chloro-Δ⁵-androsten-17-one (X) reacts with benzoate ions in molten benzoic acid to give, after hydrolysis, 3(β)-hydroxy-Δ⁵-androsten-17-one (dehydro*iso*androsterone) (XII).

The situation outlined above may be summarised as follows. Of the replacement reactions at $C_3$: (*a*) $C{\cdot}OH \xrightarrow{SOCl_2} C{\cdot}Cl$, (*b*) $C{\cdot}OH \xrightarrow{PCl_5} C{\cdot}Cl$, (*c*) $C{\cdot}Cl \xrightarrow{OAc\Theta} C{\cdot}OAc$, in the saturated series (*a*) takes place with retention and (*b*) and (*c*) with inversion of configuration, but in the Δ⁵-series all three reactions (*a*), (*b*), and (*c*) take place with retention of configuration. Whilst a reaction mechanism ($S_Ni$) is available to account for retention in (*a*), and a similar mechanism would be possible in the presence of groups able strongly to influence the geometry of the transition state (cf. the case of α-phenyl-*n*-amyl alcohol which reacts with phosphorus pentachloride with retention of configuration) but is therefore improbable here in respect of retention in (*b*), it appears impossible to invoke some analogous internal rearrangement mechanism in regard to retention in (*c*).

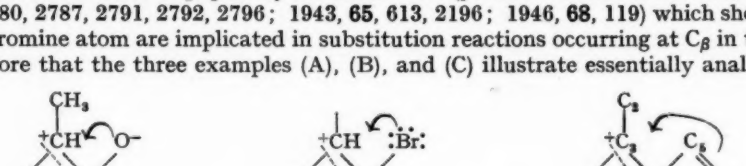
The sole constitutional feature distinguishing cholesterol and 3(β)-hydroxycholestanol, and the similar pairs of compounds referred to above, is the $C_5{:}C_6$-double bond. The incorporation of a double bond in a *cyclo*paraffin ring necessitates that the doubly-bound carbon atoms and those adjacent to them ($C_4$, $C_7$, $C_{10}$) lie in a plane, and that the angle $C_4{-}C_5{-}C_{10}$ approximates to 120°. The influence of such a structural modification is to compel rings A and B to conform more nearly to flat hexagons in cholesterol than in 3(β)-hydroxycholestanol; the general effect will be to flatten further the already nearly flat steroid nucleus, and this has been confirmed crystallographically (Crowfoot, *op. cit.*, p. 422). But since it has been shown (Part I) that the approximately planar character of the steroid nucleus facilitates the formation of a transition state of linear, as opposed to pyramidal, type and hence tends to lead to replacement with inversion of configuration, the geometrical modification arising from the introduction of a $C_5{:}C_6$-double bond can have no part in the consistent retention of configuration exhibited in the substitution reactions of compounds of the Δ⁵-series.

The conclusion is inescapable that the apparently abnormal behaviour of cholesterol and its Δ⁵-analogues must be ascribed to the polarisability of the $C_5{:}C_6$-double bond. In support of this is the interaction known to occur between $C_3$ and $C_5$ in the production of derivatives of *i*-cholestane, *i*-stigmastane, and *i*-androstane. Further, the qualitatively increased reactivity displayed by the 3-chlorine atom in cholesteryl, stigmasteryl, and sitosteryl chlorides as compared with the cholestanyl and stigmastanyl chlorides must be attributed to electron-release by the $C_5{:}C_6$-double bond, and an indication that this is so is provided by 7-ketocholesteryl chloride (XIV); Marker *et al.* (*J. Amer. Chem. Soc.*, 1937, **59**, 619) note with some surprise that the chlorine atom in this compound exhibits the qualitatively lesser reactivity characteristic of the cholestanyl and stigmastanyl chlorides, a circumstance which clearly arises from the enforced polarisation of the double bond by the 7-carbonyl group, $C_5{=}C_6{-}C_7{=}O$, in the direction opposite to that required to facilitate separation of the 3-chlorine atom. If this is true, then substitution of the 3-chlorine atom in (XIV) must proceed with inversion of configuration; and it is found (Marker *et al.*, *loc. cit.*) that the reaction of (XIV) with acetate ions in *n*-valeric acid furnishes 7-ketocholesterylene (XV) together with an acetate (XVI) which, after hydrolysis and reduction of the 7-keto-group, affords *epi*cholesterol (XVII); thus here inversion of configuration occurs in the manner characteristic of the saturated series.




* The polar influence of the 17-carbonyl group at $C_3$ is assumed to be negligible.

The suggestion that the retention of configuration uniformly observed in replacements at $C_3$ in the $\Delta^5$-series is connected with the availability of electrons at $C_3$ arising from the polarisability of the $C_5{:}C_6$-double bond leads naturally to comparison with the first-order substitution reactions of the α-bromopropionate ion (Cowdrey, Hughes, and Ingold, *J.*, 1937, 1208). At this stage during private discussion with Professor Ingold the writer's attention was directed to a series of papers by Winstein *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 1576, 1581, 1635, 2845; 1942, **64**, 2780, 2787, 2791, 2792, 2796; 1943, **65**, 613, 2196; 1946, **68**, 119) which show that the unshared electrons of an α-bromine atom are implicated in substitution reactions occurring at $C_\beta$ in the system $C_\beta$–$C_\alpha$·Br. It appeared therefore that the three examples (A), (B), and (C) illustrate essentially analogous processes.




In regard to case (A), Cowdrey, Hughes, and Ingold (*loc. cit.*) showed by a kinetically controlled stereochemical examination that the first-order hydroxylation and methoxylation reactions of the α-bromopropionate ion are unimolecular and take place with 90—100% retention of configuration by mechanism $S_N1$ without detectable racemisation. In discussing this result, Cowdrey, Ingold, Hughes, Masterman, and Scott (*J.*, 1937, 1252, especially pp. 1256 and 1261) point out that it is in conformity with theory since, owing to the anionic charge, the most stable configuration of the intermediate carbon cation is now of the pyramidal type, which corresponds to retention of stereochemical form.

Winstein, Lucas, and their collaborators (*locc. cit.*) have adduced evidence to show that OH, OAc, and OMe groups, and bromine atoms, participate in replacement reactions at an adjacent saturated carbon atom. They have discovered a case of substitution involving an intermediate cation preserved as to configuration by an α-bromine atom; they formulate an intermediate bromonium ion, using the covalent extreme for a link which Cowdrey *et al.* regard as largely electrovalent; but this makes no essential difference to the stereochemical interpretation (cf. Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 1010).

In regard to case (C), examination of the product of the substitution of the chlorine atom in cholesteryl chloride by acetate ions in acetic acid at 100° discloses 91% retention and no detectable amount (after hydrolysis) of *epi*cholesterol, and hence no detectable racemisation. The mechanism of substitution therefore appears to be exclusively $S_N1$, for although mechanism $S_N2$ was shown to operate in the case of the α-bromopropionate anion for both hydroxylation and methoxylation, this mechanism furnished 80—100% inversion of configuration, and so appears qualitatively to be excluded here. If the suggested operation of mechanism $S_N1$ may be generalised for other replacement reactions in the $\Delta^5$-series we have the following picture: as the ionisation of the group to be replaced passes over its energy barrier and before the reagent intervenes, the polarisable electrons of the $C_5{:}C_6$-double bond interact with the carbon cation sufficiently powerfully to overcome both the energetic and the geometrical factors, which normally operate to favour production of a transition state of linear type, and to lead to the formation of a transition state of pyramidal type, the consequence of which is retention of configuration following attack of the reagent and completion of the reaction.

The foregoing analysis of the facts provides a consistent picture of replacement reactions at $C_3$ in the $\Delta^5$-steroid series (case C) resting on circumstantial evidence, but no proof that the interpretation suggested is correct. An examination of the kinetics and steric orientation of nucleophilic substitutions in the simpler aliphatic analogues of case (C)—the methylallylcarbinyl and benzylmethylcarbinyl series—is being undertaken by Hughes and Ingold; and the writer hopes to make a kinetic study of some suitable replacement reaction (hydrolysis, alcoholysis, or acetolysis) of cholesteryl chloride. It is also intended to examine the chemistry of *epi*cholesterol and *cis*-dehydroandrosterone, and of *i*-cholestane and *i*-androstane derivatives, from the point of view now developed.

## Experimental.

(All m. ps. were determined thermoelectrically on a Kofler block and are therefore corrected; limit of error ±2°.)

*Acetolysis of Cholesteryl Chloride.*—Cholesteryl chloride (250 mg., chromatographically purified and recrystallised from acetone, m. p. 96°), 2 c.c. of a 20% solution of freshly fused potassium acetate in pure acetic acid, and sufficient pure acetic acid (redistilled over chromium trioxide) to give a homogeneous mixture, were heated with exclusion of moisture for 4 hours at 100°. After removal of most of the acetic acid under reduced pressure, water was added, and the product extracted with ether. The ethereal extract was washed with water, sodium bicarbonate solution, and again with water, dried ($Na_2SO_4$), and evaporated. The residue (263·5 mg.) was completely crystalline, had m. p. 112—114°, and appeared to be pure cholesteryl acetate. To confirm this, the product was heated under reflux for 0·5 hour with 4% methyl alcoholic potassium hydroxide (2·5 c.c. ≡ approx. 3 mols.); working up furnished apparently pure cholesterol, m. p. 147—148° (235 mg.), which was dissolved in methanol (7 c.c.) and treated with a solution of digitonin (700 mg.) in warm methanol (7 c.c.). Addition of water (1·4 c.c.) gave a large precipitate; the mixture was kept for 1 hour at 0°, and then separated by centrifuging. The precipitate was twice mixed with methanol and re-separated by centrifuging.

The digitonide was dried in a desiccator, dissolved in dry pyridine (4 c.c.), and decomposed by addition of dry ether (40 c.c.); the precipitated digitonin was filtered off and washed with ether, and the filtrate evaporated to yield cholesterol (217 mg.; yield, 91%), m. p. 148° after crystallisation from methanol.

The methyl alcoholic filtrates were combined and evaporated completely under reduced pressure, and the residue was extracted with boiling dry ether (5 portions of 20 c.c.); these extracts by evaporation gave a little oil (9 mg.), which was distilled at 140°/0·001 mm., and an attempt was made to crystallise the distillate from methanol. A trace of

crystalline material, m. p. 80—90° (indefinite), was obtained; it gave a positive Beilstein test for halogen and possibly consisted essentially of unchanged cholesteryl chloride.

The yield of cholesterol was 91%, that of the digitonin non-precipitatable material 3·8%; losses, which appear to be unavoidable in digitonin separations, thus amounted to about 5%.

3(β)-*Chlorocholestane from Cholesteryl Chloride.*—Cholesteryl chloride, m. p. 96° (1·00 g.), was reduced by shaking with Adams's catalyst (100 mg.) in hydrogen at atmospheric pressure for 48 hours; the solvent used was pure ethyl acetate (10 c.c.) containing pure acetic acid (0·10 c.c.) (cf. Marker, Whitmore, and Kamm, *J. Amer. Chem. Soc.*, 1935, **57**, 2358). The product obtained by filtration from the catalyst and complete evaporation had m. p. 111—112° (1·00 g.); recrystallisation from acetone afforded prisms, m. p. 112°, $[\alpha]_D^{21°}$ +18°±2° (*c*, 1·809 in chloroform), which gave a pale but distinct yellow colour with tetranitromethane. Three recrystallisations from acetone gave a product, m. p. 112—113°, $[\alpha]_D^{21°}$ +21°±2° (on material dried at 100°/10 mm.; *c*, 1·635 in chloroform), which still gave a pale yellow colour with tetranitromethane and so still presumably contained traces of unreduced cholesteryl chloride, $[\alpha]_D^{20°}$ −27° (Beynon, Heilbron, and Spring, *J.*, 1936, 907). Part of the product (330 mg.) was therefore dissolved in pure acetic acid (4 c.c.) and treated with a 2% solution of chromium trioxide in acetic acid (4 c.c. ≡ 1·5 atoms of oxygen) at 60° for 0·5 hour with efficient stirring (cf. Ruzicka, Goldberg, and Brungger, *Helv. Chim. Acta*, 1934, **17**, 1389). After working up, the neutral material was dissolved in pentane and purified from neutral oxidation products by filtration through a column of aluminium oxide (Merck–Brockmann, activity III—IV: 10 g.) prepared in pentane. After recrystallisation from acetone the pure chloro-compound had m. p. 114—115°, $[\alpha]_D^{20°}$ +27°±1° (*c*, 1·911 in chloroform).

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## 255. *A Study of the Mechanism of Oxidation with Chromic Acid.*

By WILLIAM A. WATERS.

It has been found that oxygen is absorbed during the oxidation of many organic substances with chromium trioxide in glacial acetic acid, and it is concluded therefore that the oxidation mechanism involves an initial dehydrogenation process whereby free organic radicals are generated. The oxygen uptake is regarded as a diagnostic test for the presence of these transient radicals.

Substances showing this effect include hydrocarbons, alcohols, ethers, and ketones. The significance of the observations is discussed in relation to chemical structure.

IN the course of an investigation of the mechanism of autoxidation of tetralin (Waters, *Trans. Faraday Soc.*, 1946, **42**, 184; Robertson and Waters, *ibid.*, p. 201), it was found that a rapid uptake of oxygen occurred immediately upon the addition of a small quantity of a solution of chromium trioxide in glacial acetic acid to tetralin at 76°, and that a similar catalytic effect was noticeable at room temperature. Since the autoxidation of tetralin can be depicted satisfactorily by the chain reaction sequence

$$R''CH\cdot + O_2 \longrightarrow R''CH{-}O{-}O\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

$$R''CH{-}O{-}O\cdot + R''CH_2 \longrightarrow R''CH{-}O{-}O{-}H + R''CH\cdot \quad . \quad . \quad . \quad (ii)$$

the initial product being tetralin hydroperoxide, it was suggested that chromium trioxide acted as an autoxidation chain starter by abstracting a hydrogen atom from tetralin and so forming a free hydrocarbon radical (of general type R″CH·) which, like free triphenylmethyl (compare Ziegler *et al.*, *Annalen*, 1933, **504**, 162; 1942, **551**, 213), can immediately combine with oxygen [reaction (i) above]; thus:

$$R''CH_2 + O{=}\overset{VI}{Cr}\!\!<\!\!\begin{matrix}O\\O\end{matrix} \longrightarrow R''CH\cdot + H{-}O{-}\overset{V}{Cr}\!\!<\!\!\begin{matrix}O\\O\end{matrix} \quad . \quad . \quad . \quad . \quad (iii)$$

It was therefore of interest to see whether a similar uptake of oxygen occurred during the course of other oxidations with chromium trioxide. The results of a qualitative survey of a number of oxidations of organic compounds are given in the following Tables.

From these results it is evident that oxygen uptake during the course of oxidation of organic substances is a fairly regular phenomenon, and it can be concluded therefore that the normal mechanism of oxidation by chromium trioxide is that of hydrogen abstraction to give, as the initial product, a free neutral radical.

It must be pointed out, however, that a very sensitive method of detecting gas absorption has been used, and hence the efficiencies and the chain lengths of the subsequent autoxidation processes are often very low. On the other hand oxygen uptake can only occur with those substances which can form peroxides: the peroxides of many of the substances studied are as yet unknown, whilst some of them (*e.g.*, anthracene peroxide) may dissociate. Thus absence of gas absorption during oxidation with chromic acid does not necessarily indicate that there is any difference in reaction mechanism. In a few cases slight expansions have been observed. These almost invariably concern compounds from which carbon dioxide might well be one of the final oxidation products (*e.g.*, acetophenone).

In all the reactions studied it has been evident that oxygen is absorbed by the reacting system only whilst the reduction of the chromium trioxide is actually occurring. This is most marked with the primary and secondary alcohols which have been examined (Table II). The absorption of gas by these easily oxidisable compounds is immediate, but usually stops after 15—30 minutes, after which time it can be restarted at once

TABLE I.

*Oxidation of* $CH_3$, $CH_2$, *or* CH *Groups in Hydrocarbons and Analogous Substances.*

(a) *Substances oxidised at or below* 40°.

| Compound. | Temp. used. | Result. |
|---|---|---|
| Toluene | 40° | Slow $O_2$ absorption continuing over a long period. |
| *p*-Nitrotoluene | 40 | " " " " " " |
| *m*-Xylene | 40 | Definite $O_2$ absorption. |
| *p*-Xylene | 40 | " " " |
| Ethylbenzene | 20 | " " " |
| *iso*Propylbenzene | 20, 40 | Some gas evolution for first hour followed by marked gas absorption. |
| Diphenylmethane | 35 | Definite $O_2$ absorption. |
| Triphenylmethane | 20, 45 | Slow oxidation combined with a *slight* evolution of gas. |
| Fluorene | 15 | Slow oxidation } with *slight* expansion. |
| | 35 | Rapid oxidation } |
| Acenaphthene | 20 | Very definite $O_2$ absorption. |
| Anthracene | 40 | Rapid oxidation; gas uptake indefinite. |
| Phenanthrene | 35 | Slow $O_2$ uptake over long period. |
| Triphenylethylene | 18 | Marked $O_2$ absorption. |
| Decalin (mainly *trans*-) | 20 | Slow $O_2$ uptake over long period; slow oxidation. |
| *cyclo*Hexene | 40 | Rapid reaction with marked $O_2$ absorption; completed in 5 mins. |
| Oleic acid | 40 | Steady $O_2$ absorption during 2 hours; oxidation then completed. |
| Phenylacetic acid | 40 | Evolution of $CO_2$ masked observation. |

(b) *Substances not oxidised at* 40°. Methyl*cyclo*hexane; ethyl*cyclo*hexane; 2 : 2 : 5-trimethylhexane; α-picoline; quinaldine; acetic acid; succinic acid; adipic acid.

TABLE II.

*Oxidation of Alcohols and Ethers.*

| Compound. | Temp. used. | Result. |
|---|---|---|
| Benzyl alcohol | 20° | Marked $O_2$ absorption which ceased when all $CrO_3$ had been reduced (30 mins.). |
| β-Phenylethyl alcohol | 20 | Marked $O_2$ absorption which ceased when all $CrO_3$ had been reduced (1 hour). |
| *n*-Butyl alcohol | 20 | Marked $O_2$ absorption which ceased when all $CrO_3$ had been reduced. |
| *sec.*-Butyl alcohol | 20 | " " " " " " " " |
| *n*-Amyl alcohol | 20 | " " " " " " " " |
| *cyclo*Hexanol | 20 | Definite, but much slighter $O_2$ uptake. |
| Benzhydrol | 20 | $O_2$ uptake definite with carbinol in excess, but not with $CrO_3$ in excess; violet-red product. |
| Ethyl lactate | 20 | Definite $O_2$ absorption. |
| Triphenylcarbinol | 40 | Slow evolution of gas; slow oxidation (cf. triphenylmethane, Table I). |
| *tert.*-Butyl alcohol | 40 | Very little oxidation, but slight gas production. |
| Benzyl methyl ether | 40 | Marked $O_2$ absorption continuing over a long period. |
| *n*-Butyl ether | 40 | Definite $O_2$ absorption, continuing over a long period. |
| *iso*Propyl ether | 20 | Very slight reaction with some sign of $O_2$ uptake. |
| Phenetole | 40 | Very slow oxidation; no evident gas absorption. |

TABLE III.

*Oxidation of Ketones and Esters.*

(a) *Substances oxidised at or below* 40°.

| Compound. | Temp. used. | Result. |
|---|---|---|
| Methyl ethyl ketone | 40° | Definite $O_2$ absorption, continuing over some hours. |
| Acetophenone | 40 | Gas evolution (? $CO_2$; cf. phenylacetic acid). |
| Menthone | 40 | Definite $O_2$ absorption over 2-hour period. |
| *cyclo*Hexanone | 40 | Slow $O_2$ absorption over long period. |
| α-Tetralone | 40 | Slight expansion. |
| Ethyl acetoacetate | 40 | Definite $O_2$ absorption; reaction almost completed in 30 mins. |
| Ethyl cinnamate | 40 | Very slow oxidation; slight expansion. |

(b) *Substances not oxidised at* 40°. Camphor; ethyl malonate; ethyl phenylacetate; ethyl cyanoacetate; ethyl dichloroacetate; *n*-butyl benzoate; *sec.*-butyl benzoate; *cyclo*hexyl acetate.

TABLE IV.

*Other Substances.*

(a) *Substances oxidised at* 40°. Benzyl cyanide. Slow $O_2$ uptake during some hours; oxidised. Piperidine (as acetate). Very slight $O_2$ absorption; very slight oxidation.
(b) *Substances not oxidised at* 40°. Benzylamine; di-*n*-butylamine (as their acetates).

by adding a little more chromium trioxide. The gas absorption is not therefore due to the production of an oxidation product of long free life, such as an aldehyde.

Most of the oxidisable substances listed in Table I are known to yield hydroperoxides by direct, or heavy-metal-catalysed autoxidation (for refs. see Waters, *Ann. Reports*, 1945, **42**, p. 131 *et seq.*), but it is interesting to note that oxygen uptake during oxidation is not confined to substances such as toluene, diphenylmethane, or

*cyclo*hexene which contain active methylene groups, but includes substances such as triphenylethylene and phenanthrene in which oxidation must affect a >C=CH— group.

The results listed in Table II are of particular interest, since they show that the oxidation of both primary and secondary alcohols follows the dehydrogenation mechanism. For this two routes can be envisaged:

$$R''C\begin{matrix}H\\O-H\end{matrix} \longrightarrow R''\dot{C}-OH \rightleftharpoons H^+ + R''\dot{C}-O^- \quad . \quad . \quad . \quad . \quad (iv)$$

*mesomeric radical-anion*

$$R''C\begin{matrix}H\\O-H\end{matrix} \longrightarrow R''C\begin{matrix}H\\O\cdot\end{matrix} \rightleftharpoons H^+ + R''\bar{C}-O\cdot \quad . \quad . \quad . \quad . \quad (v)$$

of which only reaction (iv) can easily be conceived as leading to a hydroperoxide of known type, *viz.*

$$R''\dot{C}-OH + O_2 \longrightarrow R''C\begin{matrix}OH\\O-O-H\end{matrix} \quad . \quad . \quad . \quad . \quad . \quad (vi)$$

*etc.*

The initial radical postulated in process (iv) has the electronic structure of a free ketyl radical (compare $Ph_2\dot{C}-\bar{O}Na^+$), but since the removal of a proton from either the radical of reaction (iv) or that of reaction (v) would yield a *mesomeric* radical-anion it may be difficult, if not impossible, to discriminate experimentally between the two processes. The first stage of reaction (v) should be possible with a tertiary alcohol, though the product, $R_2C-O\cdot$, would not be expected to take up oxygen. Oxygen absorption has not, in fact, been noted in this case.

Some ethers absorb oxygen on oxidation, although they react much more slowly than do the corresponding alcohols; this must undoubtedly be due to attack at a C–H group, as in reaction (iv). In contrast, esters of these same alcohols with stable acids, such as benzoic or acetic acid, are resistant to oxidation.

Table III shows that oxygen is absorbed during the oxidation of some ketones. Since these are substances which are oxidised more easily than are the corresponding paraffinic hydrocarbons the reaction may perhaps be one in which the enolic form is concerned.

Whilst all the oxidations which have been studied in this investigation can consistently be interpreted as reactions involving dehydrogenation, it is significant that the ease of oxidation of an organic compound with chromium trioxide does not follow the sequence of ease of proton ($H^+$) removal. Thus ethyl malonate, ethyl phenylacetate, and ethyl cyanoacetate resist oxidation at 40°. Any oxidation of course involves electron abstraction, and the ease of removal of this electron is evidently the rate-controlling feature, since strongly electron-attracting groups in the organic molecule, such as carbethoxy or quaternary nitrogen, stabilise it. It does not follow, however, that ease of oxidation by homolytic separation of hydrogen atom (proton *plus* an electron) and ease of dissociation as an acid (proton release) should be converse processes, since other structural features have to be considered. For instance the oxidisability of benzyl cyanide, like that of toluene or of diphenylmethane, may be due to the possibility of formation of a mesomeric (*i.e.*, resonance stabilised) substituted benzyl radical. Again, the formation of a mesomeric radical can be invoked as the reason for the oxidisability of alcohols (see above).

Any homolytic dehydrogenation can be written as a one-stage process (*e.g.*, iii) or alternatively (cf. Weiss, *Trans. Faraday Soc.*, 1946, **42**, pp. 116, 122) as a two-stage process comprising

(*a*) Reversible ionisation of proton: $R''CH_2 \rightleftharpoons H^+ + (R''CH:)^-$

(*b*) Electron abstraction: $(R''CH:)^- + Ox \longrightarrow R''CH\cdot + Red.$*

If this two-stage process of (*a*) followed by (*b*) were the true reaction sequence then facile proton release (*a*) should be conducive to oxidisability, for otherwise (*b*) could never occur. This does not accord with experimental fact. The hypothesis, for instance, would indicate that ethyl malonate should easily be oxidised, since with it stage (*a*) is easy, and so should be stage (*b*), since the anion, which occurs in ethyl sodiomalonate, is oxidised at room temperature by molecular iodine, which has a very low oxidation potential; *e.g.*

$$2CHNa(CO_2Et)_2 + I_2 \longrightarrow 2NaI + (EtO_2C)_2CH-CH(CO_2Et)_2$$

In order to formulate a bimolecular sequence in the reverse order

(*c*) $R''CH_2 + Ox \longrightarrow (R''CH_2)^+ + Red$

(*d*) $(R''CH_2)^+ \rightleftharpoons H^+ + (R''CH\cdot)$

it is necessary to postulate the existence of radical-cations of simple paraffins in which one covalency has been converted into a single-electron bond. As yet such radical-cations have been encountered only in the "aminium salts," or in complex aromatic ring systems—both being structures derived from molecules in which all the valency electrons are not originally concerned in single bond (C–C or C–H) formation. The postulation of oxidation by one-stage removal of a hydrogen atom is thus both more satisfactory and more simple.

* Following standard nomenclature: $e + Oxidiser \rightleftharpoons Reducer.$

Equation (iii) might be taken as suggesting that the reduction of chromium trioxide to a chromic salt involves the stepwise conversion of $Cr^{VI}$ to $Cr^{III}$ by three successive electron-accessions to the chromium atom. Whilst this view has already been put forward both by Luther (*Z. physikal. Chem.*, 1903, **46**, 777; *Z. anorg. Chem.*, 1907, **54**, 1) and by Wagner (*Z. physikal. Chem.*, 1924, **113**, 261; *Z. anorg. Chem.*, 1928, **168**, 265, 279) to explain certain features of the kinetics of oxidations involving aqueous chromic acid, it is not an essential part of the homolytic theory of oxidation by dehydrogenation. In connection with this earlier work, however, it is cogent to note that Wagner (*Z. anorg. Chem.*, 1928, **168**, 279) showed that, whilst acidified potassium dichromate does not react with potassium iodide in the presence of a sodium bicarbonate or sodium acetate buffer, some iodine is liberated if a reacting mixture of acidified chromic and oxalic acids is poured into a similar buffered solution. Reacting mixtures of chromic and lactic acids react even more noticeably with buffered iodide solutions. These curious observations can now be interpreted as being reactions in which short-lived organic radicals are concerned.

### Experimental.

A simple form of Barcroft's differential manometric apparatus was constructed by connecting the side-arms of two stoppered distilling flasks (*A* and *B*), of similar capacity (150 ml.), to the two limbs of a manometer filled with butyl phthalate, and fitting between the flasks a glass tap, by means of which the internal pressures could, if required, be equalised. The flasks were both immersed in a thermostat in which they were shaken periodically.

Into flask *A* were placed the substance to be investigated (usually 5 ml.) and glacial acetic acid (usually 20 ml.) previously stabilised by distillation from chromic acid. Into flask *B* were placed the same quantity of the substance and acetic acid (usually 25 ml.) taken from the same stock. A solution of pure chromium trioxide in the same acetic acid was also placed in the thermostat. When temperatures had equalised, and no manometric shift could be noted, chromium trioxide solution (5 ml.) was pipetted into flask *A*, so that the total volume of solvent in this flask was then the same as in flask *B*. Flask *A* was then stoppered, the air pressures in the flasks were equalised, and the interconnecting tap was closed.

Absorption of gas in *A* was easily observable as a progressive shift in the manometer level. From time to time the gas pressures in the flasks were momentarily equalised: a consistent pressure change over a period then indicated continuing gas absorption and not transient effects due to thermal irregularities, etc. "Definite oxygen absorption" in Tables I—III corresponds to a shift of manometric levels of over 2 cm. per hour. It was often very much more, and sometimes measured in centimetres per minute.

The observations with each substance were always carried out more than once, the reaction flasks being chosen at random. Particular care was taken in the purification of the substances. The purified acetic acid had no reducing action on chromium trioxide over a period of weeks. The organic substances were either distilled to constant b. p., with rejection of large head and tail fractions, or else crystallised repeatedly. In cases of doubt observations were repeated after further purification.

The author thanks Messrs. Imperial Chemical Industries Ltd. (Billingham Division) for the gift of specimens of some pure hydrocarbons.

The Dyson Perrins Laboratory, Oxford. [*Received, April 10th*, 1946.]

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## 256. *Decomposition Reactions of the Aromatic Diazo-compounds. Part XI. The Mechanism of Formation of Azo-compounds, Polyaryls, and Aryl Sulphides.*

By K. H. Saunders and William A. Waters.

The appearance of azo-compounds and polyaryls among the products of decomposition of diazo-compounds in aqueous solution near the neutral point in the presence of a mild reducing agent, and the conversion of 2 : 2′-tetrazodiphenyl into diphenylazone, indicate that in part diazo-compounds can undergo decomposition of Type II (Waters, *J.*, 1942, 266) in aqueous solution, giving free aryl radicals which may, among other reactions, either (*a*) react with diazo-kations with single electron transfer from the reducing agent giving a symmetrical azo-compound, or (*b*) attack undecomposed covalent diazo-compounds giving a diazodiaryl compound which, by a similar decomposition in the tar phase, eventually yields polyaryls, or combines as in (*a*) to form an arylazodiaryl. There is also evidence to suggest that diazo-sulphides undergo homolysis in aqueous media to produce radicals.

There are a number of decomposition reactions of the aromatic diazo-compounds for the mechanism of which no satisfactory hypotheses have yet been advanced. Among these may be mentioned (1) the production of symmetrical azo-compounds by the reduction of benzenoid diazo-compounds free from negative substituents [in especially high yield from diazotised ψ-cumidine and *as.*-*m*-xylidine in the presence of ammoniacal cuprous oxide (Vorländer and Meyer, *Annalen*, 1901, **320**, 122)]; (2) formation of both azobenzene and benzeneazodiphenyl from benzenediazonium salts in the presence of potassium ferrocyanide (Griess, *Ber.*, 1876, **9**, 132; Locher, *ibid.*, 1888, **21**, 911); (3) formation of diphenyl sulphide together with benzeneazodiphenyl from benzenediazonium salts by interaction with sodium cupro-thiosulphate (Börnstein, *Ber.*, 1901, **34**, 3968) and (4) the closure of the diphenylazone ring by the action of cuprous bromide (Dobbie, Fox, and Gauge, *J.*, 1911, **99**, 1615) or sodium arsenite (Sandin and Cairns, *J. Amer. Chem. Soc.*, 1936, **58**, 2019) on tetrazotised 2 : 2′-diaminodiphenyl.

In the general scheme previously put forward by one of us (Waters, *loc. cit.*), the homolysis of undissociated diazo-compounds into two free radicals with liberation of nitrogen was regarded as occurring regularly only in non-dissociating solvents (compare Grieve and Hey, *J.*, 1938, 109), though the production of a trace of benzene

from a faintly alkaline solution of diazobenzene hydroxide (Waters, *J.*, 1937, 2016) showed that radical formation in aqueous solution (i), and subsequent decomposition as in (ii), is not quite impossible : *

$$Ar{:}\dot{N}{=}\dot{N}{:}X \longrightarrow Ar^{\star} + {:}N{\equiv}N{:} + X^{\star} \quad . . . . . \text{(i)}$$
$$Ar^{\star} + H_2O \longrightarrow Ar{-}H + {}^{\star}OH \quad . . . . . \text{(ii)}$$

However, the fact that diaryls, sometimes mixed with symmetrical azo-compounds, can be formed in good yield by the action of ammoniacal cuprous oxide on negatively-substituted aromatic diazo-compounds, indicates that many diazo-compounds can be converted, in part at least, into free radicals in aqueous solution. The source of these radicals must be the undissociated diazo-hydroxide molecules, which at any time comprise

$$Ar{-}\overset{+}{\dot{N}}{=}N{:}\ \underset{X^-}{} \rightleftharpoons Ar{-}\dot{N}{=}\dot{N}{-}X \rightleftharpoons Ar{-}\dot{N}{=}\dot{N}{-}OH \quad . . . . . \text{(iii)}$$
(X = any anion)

only a part of the diazo-compound present, though near the neutral point the equilibrium will tend to favour the diazo-hydroxide form, the actual percentage present being dependent both on the pH of the solution and on the nature of the aryl group concerned.

Shortly after decomposition commences in one of the above mixtures there is thus present, distributed at random through the solution, a certain amount of diazo-hydroxide which has broken up into free radicals, as in (i), which besides reacting with water molecules [as in (ii)], might combine with dissociated diazo-kations, the reducing agent supplying the necessary electron to produce a symmetrical azo-compound by the reaction

$$Ar^{\star} + ArN_2^+ + e \longrightarrow Ar{-}N_2{-}Ar \quad . . . . . \text{(iv)}$$

Whether ammoniacal cuprous oxide will convert a given diazo-compound into an azo-compound, or into a diaryl, is therefore determined by the amount of the undissociated diazo-hydroxide present under the given conditions, and upon the mean life of the free aryl radical. If the amount of undissociated hydroxide is large, many free aryl radicals are formed and hence the yield of diaryl will be high. This corresponds with the fact that negative substituents drive the equilibrium (iii) to the right. The formation of αα′- and ββ′-azonaphthalene by reduction of α- and β-diazonaphthalenes, for example, with alkaline sulphite (Lange, D.R.-P. 78,225; "Friedländer," **4**, 1016) should perhaps be excluded from this discussion, because there is no *a priori* evidence (*e.g.*, the isolation also of diaryls or of azo-diaryls) that free radicals are concerned. The formation of *s*-azo-nitronaphthalenes in strongly acid solution with cuprous oxide as a reducing agent has been ascribed to the union of free aryl radicals with free diazo-radicals (Hodgson, *J.*, 1942, 744), the latter being formed by the prior acceptance of an electron by a diazonium ion :

$$Ar{-}\overset{+}{\dot{N}}{=}\dot{N}{:} + e \longrightarrow Ar{-}\dot{N}{=}\dot{N}^{\star} \quad . . . . . \text{(v)}$$
$$Ar^{\star} + {}^{\star}\dot{N}{=}\dot{N}{-}Ar \longrightarrow Ar{-}\dot{N}{=}\dot{N}{-}Ar \quad . . . . . \text{(vi)}$$

a mechanism entirely different from that [equation (iv)] contemplated here, and one which we regard as improbable, since the driving force in the homolysis of the covalent diazo-compounds is the elimination of molecular, stable, nitrogen gas which leads to the *simultaneous* production of *two* neutral radicals.

In reactions (2) and (3) some of the free phenyl radicals must concurrently attack the undissociated benzenediazo-hydroxide :

$$Ph^{\star} + Ph{-}N_2{-}OH \longrightarrow Ph{-}C_6H_4{-}N_2{-}OH + H^{\star} \quad . . . . . \text{(vii)}$$

The molecule of diazodiphenyl hydroxide thus formed then can decompose into a diphenyl radical, $Ph{-}C_6H_4^{\star}$, which by combination with a diazobenzene kation, as in (iv), yields an arylazo-diaryl under the influence of the reducing agent :

$$Ph{-}C_6H_4^{\star} + Ph{-}N_2^+ + e \longrightarrow Ph{-}C_6H_4{-}N_2{-}Ph \quad . . . . . \text{(viii)}$$

Alternatively, however, benzeneazodiphenyl may be produced by combination of a phenyl radical with dissociated diazodiphenyl hydroxide (as in ix) :

$$Ph^{\star} + Ph{-}C_6H_4{-}N_2^+ + e \longrightarrow Ph{-}C_6H_4{-}N_2{-}Ph \quad . . . . . \text{(ix)}$$

In reduction by potassium ferrocyanide, the azobenzene is produced by (iv), while a third compound, an oil of unknown constitution, is also mentioned by Griess (*loc. cit.*) and provides further evidence of that multiplicity of products which often characterises free radical reactions. In Börnstein's reaction (3) the diphenyl sulphide may arise from a similar union of phenyl radicals with thiophenol (x).

$$Ph^{\star} + H{-}S{-}Ph \longrightarrow Ph{-}S{-}Ph + {}^{\star}H \quad . . . . . \text{(x)}$$

Graebe and Mann's account (*Ber.*, 1882, **15**, 1683) of the production of diphenyl sulphide, diphenyl disulphide, and sulphur from benzenediazonium salts and hydrogen sulphide, or ammonium sulphide, supplies evidence

* Dots represent electrons, an asterisk the single electron of a free radical, and a dash a covalent link.

for the formation of free radicals by the homolysis of diazobenzene hydrogen sulphide, a substance well-known for its instability (Griess, *Annalen*, 1866, **137**, 74). The following reactions can then all occur:

$$Ph{:}\dot{N}{=}\dot{N}{:}SH \longrightarrow Ph^{*} + {:}N{\equiv}N{:} + {*}SH$$
$$Ph^{*} + {*}SH \longrightarrow Ph{-}SH$$
$$Ph^{*} + Ph{-}SH \longrightarrow Ph{-}S^{*} + Ph{-}H \quad \text{[as an alternative to (x)]}$$
$$2Ph{-}S^{*} \longrightarrow Ph{-}S{-}S{-}Ph;\ 2HS^{*} \longrightarrow H_2S_2$$

The oxidation of the hydrogen sulphide to $H_2S_2$ and thence to sulphur is strongly diagnostic of a Type II reaction (cf. Waters, *J.*, 1937, 2015; 1942, 266).

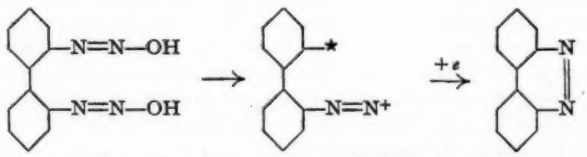
The formation of " diazo-resins " is also to be explained on these lines, for when the aromatic reaction products separate from the aqueous phase they will, like the non-aqueous phase in the Gomberg reaction (Grieve and Hey, *loc. cit.*), then extract free radicals, or their precursors, from the solution, thereby building up by subsequent homolytic reactions the chain-molecules which form the deeply-coloured, nitrogen-containing resins so often observed. Indeed, Angeli and Jolles (*Gazzetta*, 1931, **61**, 403) have already suggested that the diazo-resins are related, in their mode of formation, to benzeneazodiphenyl. Further, the non-aqueous phase is the probable site of formation of polyphenyls which, it may be noted, can be produced by the reduction of benzenediazonium salts in alcohol with copper (cf. Gerngross, Schashnow, and Jonas, *Ber.*, 1924, **57**, 747). The polyphenyls, which are obtained in poor yield, can be built up from free phenyl and diphenyl radicals formed by homolysis of diazobenzene hydroxide and of diazodiphenyl hydroxide:

$$Ph^{*} + Ph{-}C_6H_4{*} = Ph{-}C_6H_4{-}Ph$$
$$Ph{-}C_6H_4{*} + Ph{-}C_6H_4{*} = Ph{-}[C_6H_4]_2{-}Ph$$

and alternatively, or concurrently, by reactions such as:

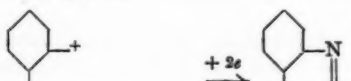
$$Ph^{*} + C_6H_6 \longrightarrow Ph_2 + H^{*}$$
$$Ph^{*} + Ph_2 \longrightarrow Ph{-}C_6H_4{-}Ph + H^{*}.$$

The formation of diphenylazone can best be explained by the following scheme, which is analogous to reaction (iv).




. . . . . (xi)

It is possible that in the acid solution of Dobbie, Fox, and Gauge's experiment an aryl kation is first formed by a heterolytic fission of Type I (Waters, *loc. cit.*) and that ring closure then takes place by the simultaneous transfer of two electrons from the reducing agent:




. . . . . (xi)

An aryl kation would, however, tend to combine at once with an anion from the solution, and as it is difficult to replace the diazo-groups in 2 : 2′-tetrazodiphenyl by chlorine or bromine in aqueous solution the free radical mechanism (x) with a single electron-transfer from the cuprous salt is more probable.

This discussion leaves out of account the yet unsolved question as to how different reducing agents affect the free radical reactions, so that from the same diazo-compound different end-products may result, though probably the solubility of the electron-donor and its oxidation–reduction potential are the key factors; insoluble donors promote reaction in a non-aqueous phase, while soluble donors promote reaction in solution.

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## 257. *The Photochemical Instability of* cis- *and* trans-4 : 4′-*Diamidinostilbene.*

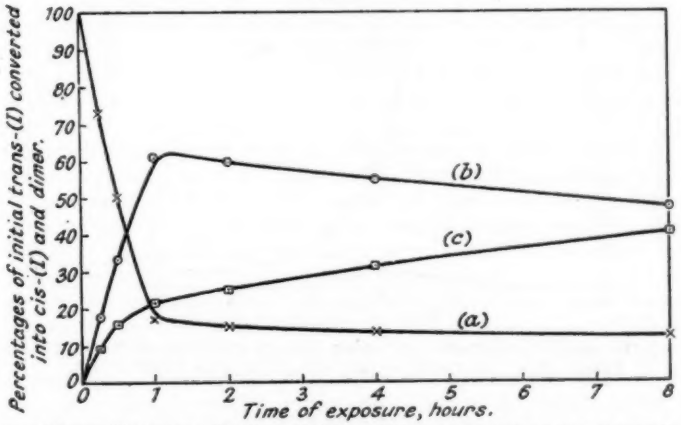
By Alan J. Henry.

Aqueous solutions of *trans*-4 : 4′-diamidinostilbene [*trans*-(I)] on insolation undergo two concurrent changes—dimerisation and *cis–trans* isomerisation—the proportion in which the products of the two reactions are formed being dependent upon both concentration and temperature. At all concentrations and temperatures the reactions proceed until equilibrium is established between the *cis*- and *trans*-forms, the equilibrium thereafter slowly drifting owing to conversion of the latter into the dimer. The dimerisation of *trans*-(I) is only very slightly reversible in sunlight, but under the influence of short ultra-violet waves (*ca.* 2500 A.) reversal of dimerisation is rapid and substantial, equilibrium being ultimately established. *Cis*-(I) has no tendency to

dimerise except indirectly *via trans*-(I). The yellow colour developing on irradiation of *trans*-(I) is attributed to a secondary reaction product of *cis*-(I), produced from *trans*-(I). The product of the dimerisation of *trans*-(I) is strongly adsorbed by filter-paper and can be estimated fluorimetrically. Solutions of *trans*-(I) fluoresce in both the blue and the green-yellow of the spectrum, the former preponderating at low, and the latter at intermediate, concentrations. The fluorescence exhibits marked concentration- and temperature-quenching.

INCREASED toxicity of solutions of *trans*-4 : 4′-diamidinostilbene (stilbamidine) [*trans*-(I)] on exposure to sunlight was first reported by Fulton and Yorke (*Ann. Trop. Med. Parasit.*, 1942, **36**, 134), and has since been confirmed by Barber, Slack, and Wien (*Nature*, 1943, **151**, 107), Fulton (*Ann. Trop. Med. Parasit.*, 1943, **37**, 48), and Kirk and Henry (*ibid.*, 1944, **38**, 99). The increase in toxicity is also accompanied by decrease in trypanocidal activity (Fulton, *loc. cit.*), pronounced modification of the absorption spectrum (Goodwin, *Ann. Trop. Med. Parasit.*, 1943, **37**, 59), and reduction in capacity for reacting with bromine and permanganate (Barber *et al.*, *loc. cit.*; Fulton, *loc. cit.*). The monomethyl derivative of *trans*-(I) was found to be affected by irradiation in a closely similar way, and 4 : 4′-diamidinotolane underwent a two-fold increase in toxicity and marked yellowing on irradiation. The 4 : 4′-diamidines of the dimethyl derivative of *trans*-(I) and of the saturated compounds 1 : 3-diphenoxypropane, 1 : 5-diphenoxypentane, and 1 : 2-diphenylethane showed no significant modification of toxicity, trypanocidal activity, or absorption spectrum on irradiation, though the first developed a strong yellow colour.

FIG. 1.




*Insolation of* 0·2% *soln. of* trans-(I) *hydrochloride. Solution* (47 *c.c.*) *contained in "Pyrex" flasks*, 50 *c.c. capacity. Temp.*, ca. 48°. trans-(I) = (*a*); cis-(I) = (*b*); *dimer* = (*c*).

From the effect upon the chemical and physical properties of *trans*-(I) it was clear that it was the ethylenic linkage which was affected by the irradiation, resulting in saturation of the compound. The reaction occurring was considered by Barber *et al.* (*loc. cit.*) to be the addition of water at the ethylenic linkage with formation of 4 : 4′-diamidinophenylbenzylcarbinol (II). This assumption appeared to explain all the known facts, including Fulton's (*loc. cit.*) finding that irradiation and subsequent desiccation yielded a product whose composition corresponded to addition of water to *trans*-(I), and strong supporting evidence was produced by them. Goodwin (*loc. cit.*) pointed out that, while the modification of the absorption spectrum was in conformity with this view, the observed results would equally well be explained by any process involving saturation of the ethylenic linkage. He also pointed out that the stilbene derivatives can obviously exhibit *cis–trans*-isomerism, but added: " . . . in the case of the parent substance the isomerides show different band intensities rather than any marked change in position. Although this type of isomerism probably plays a part in determining the photochemical reactivity of the compounds, the slight effect which may be shown in their spectra can, at this stage, be ignored ". Barber *et al.* (*loc. cit.*) considered *cis–trans*-isomerisation as a possibility, but decided against its occurrence.

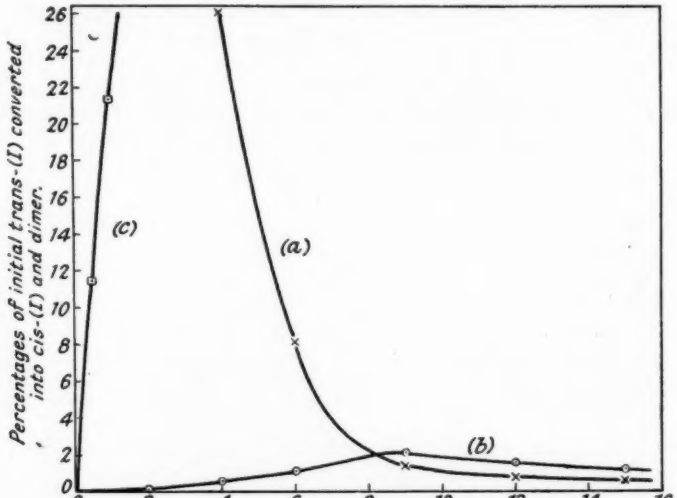
The present author's preliminary experiments with freshly prepared 1% solutions of *trans*-(I) hydrochloride exposed to direct tropical sunlight confirmed the partial conversion into a very soluble bromine-absorbing compound capable of giving rise to a blue fluorescence, similar to that of the parent compound, on exposure to ultra-violet light, and it seemed very probable that this compound was *cis*-(I), which would be expected to be more soluble than the *trans*-isomer. At the same time examination of the saturated irradiation product appeared to throw doubt upon its being (II), and to indicate that it was a product of the dimerisation of (I). In consequence the view was put forward (Henry, *Nature*, 1943, **152**, 690) that the main reactions occurring on irradiation were dimerisation, giving 1 : 2 : 3 : 4-tetra-(4′-amidinophenyl)*cyclo*butane (III), and *cis–trans*-isomerisation (cf. also Kirk and Henry, *loc. cit.*). Shortly after the publication of these views Devine (*Ann. Trop. Med. Parasit.*, 1944, **38**, 35) put forward similar views without, however, giving fresh supporting evidence.

It was suggested (Henry, *loc. cit.*) that the primary photochemical reaction might be *cis–trans*-isomerisation followed by dimerisation of the resulting *cis*-isomer, as normally being the more reactive of the two forms. From the shapes, at all concentrations, of the experimental curves (cf. Figs. 1 and 2) in the immediate vicinity

of the origin it is evident, however, that this is not the case, and that the two products arise independently, and directly, from the original *trans*-(I). In point of fact *cis*-(I) shows no tendency to dimerise except indirectly *via trans*-(I) (*vide infra*).

*Trans*-(I) has a strong blue fluorescence in dilute solution and when absorbed in filter-paper, and its fluorescent and adsorptive properties have been made the basis of an approximate method of estimation applicable to dilute solutions in water and in the biological fluids (Henry and Grindley, *Ann. Trop. Med. Parasit.*, 1942, **36**, 102; 1945, **39**, 1). It also absorbs bromine quantitatively, and the conditions necessary for its accurate bromometric estimation have been determined (Henry, *J.*, 1945, 870).

FIG. 2.




*Insolation of* 15% *soln. of* trans-(I) *isethionate. Solution* (30 *c.c.*) *contained in "Pyrex" flasks,* 50 *c.c. capacity. Temp.*, 45°. trans-(I) = (*a*); cis-(I) = (*b*); *dimer* = (*c*).

## DISCUSSION.

Insolation of neutral solutions of *trans*-(I) gives rise to two principal irradiation products in proportions depending on both concentration and temperature. The principal irradiation product at low concentrations is unsaturated and develops fluorescence on exposure to light, and it and *trans*-(I) are freely interconvertible by irradiation in solution, *via* an equilibrium which, at constant temperature, is independent of concentration. There can therefore be no doubt that this irradiation product is *cis*-(I), and failure of previous workers to detect it is attributable to the conditions—fairly low concentration and rather elevated temperature—required for its formation in substantial proportion.

The principal insolation product at higher concentrations is saturated and non-fluorescent, and is presumably the same product as that which Barber *et al.* consider to be (II). Concurrent formation of (II) and *cis*-(I) from *trans*-(I) should produce the two compounds in ratio independent of concentration, since each would be in effect the result of a unimolecular reaction. That this ratio is definitely not independent of concentration is strong evidence against the validity of the theory that the saturated product is (II). Furthermore, if hydration at the ethylenic linkage can occur at all it is not easy to see why it does not do so at low concentrations. Anhydrous *trans*-(I) isethionate can be converted, by insolation of very concentrated solutions at low temperature, almost quantitatively into the anhydrous, saturated irradiation product *without change in weight*, so disproving carbinol formation and showing polymerisation or an intramolecular change involving saturation, for which there seems no reasonable mechanism. Since the kinetics of the photochemical reaction favour dimerisation as opposed to formation of a higher polymer, there is little doubt that the saturated product is (III), the dimer of *trans*-(I), and this is assumed henceforth. The salts of these compounds are highly ionised in aqueous solution, have low solubilities in ethanol, and the free bases are nearly insoluble in the usual organic solvents. Direct proof of dimerisation by molecular weight determinations therefore appeared too unpromising and was not attempted.

The *cis–trans*-change is freely reversible in direct sunlight, diffuse daylight, and the filtered light (3000—4000 A.) of the mercury lamp. Under these conditions of irradiation the dimerisation reaction shows signs of being only slightly reversible even at high concentrations, but under the influence of the unfiltered light of the mercury lamp reversal of dimerisation, both in solution and when adsorbed on filter-paper and dried, is rapid. There is evidence that reversal of dimerisation produces *trans*-(I) only, and that equilibrium is ultimately established between dimer and *trans*-(I) on the one hand and *trans*-(I) and *cis*-(I) on the other. Reversal of dimerisation is effected by light of frequency 2700—2400 A., which coincides with the absorption band of the

irradiation product found by Goodwin (*loc. cit.*). Filtration of the light through a 1% solution of the dimer effectively removes the wave-lengths responsible for the reversal of dimerisation.

Since none of these reactions takes place to any detectable extent in the dark it is concluded that all of the compounds concerned are thermo-stable, and that, at room temperature at any rate, all of the reactions are photochemical only. They may be summarised as follows, in which T, C, and D refer to *trans*-(I), *cis*-(I) and dimer respectively, and * to activated forms :

$$T + h\nu_1 \longrightarrow T^* \quad . . . . . \quad (1)$$

$$T^* \longrightarrow T + h\nu_1 \text{ (fluorescence emission)} \quad . . . . . \quad (2)$$

$$T^* \longrightarrow C \quad . . . . . \quad (3)$$

$$T^* + T \longrightarrow D \quad . . . . . \quad (4)$$

$$C + h\nu_2 \longrightarrow C^* \longrightarrow T \quad . . . . . \quad (5, 6)$$

$$D + h\nu_3 \longrightarrow D^* \longrightarrow 2T \quad . . . . . \quad (7, 8)$$

Reaction (3) tends to reduce the fluorescence efficiency at all concentrations, and reaction (4) readily accounts for the marked concentration-quenching which *trans*-(I) exhibits. Neither *cis*-(I) nor the dimer fluoresces in the visible spectrum, but each develops fluorescence on suitable irradiation due to partial conversion into *trans*-(I).

Owing to the almost complete irreversibility of dimerisation in sunlight *trans*-(I) continues to dimerise after equilibrium between *trans*-(I) and *cis*-(I) has been established. In consequence a steady decrease in concentration of both forms occurs, but the ratio of the two remains constant at a value of 4—5, independent of the initial concentration over the range 1·0—0·02%. On insolation of concentrated solutions of *trans*-(I) isethionate, values of the final equilibrium *cis*-(I)/*trans*-(I) ratio much lower than the above are obtained. This is attributed to slight reversal of dimerisation, confirmed by prolonged insolation of spots of dimer solution on filter paper, maintaining the *trans*-(I) concentration at a higher value than corresponds to the true equilibrium value. Insolation of these solutions after dilution to 1% results in rapid readjustment of the *cis*-(I) and *trans*-(I) concentrations to give the *cis*/*trans* ratio characteristic of the diluted solutions.

Variation with temperature of the dimer/*cis*-(I) ratio for the early stages of insolation of solutions (0·2%) of *trans*-(I) hydrochloride shows that at low temperatures very little *cis*-(I) would be produced at this concentration, and that the dimer/*cis*-(I) temperature curve approximates to a rectangular hyperbola. It is not known whether a similar relationship holds for other concentrations. At constant initial concentration of *trans*-(I) the rate of conversion of *trans*-(I) into *cis*-(I) and dimer is, in the early stages of the reaction, approximately independent of the temperature, and depends only upon the amount of light received. Each molecule of dimer produced, however, results from combination of one activated molecule of *trans*-(I) with one unactivated molecule [reaction (4)]. The total proportion of primarily activated *trans*-(I) molecules which are deactivated by conversion into *cis*-(I) and dimer is therefore represented by the sum of the *cis*-(I) and half of the dimer produced. This sum increases (Table II) as the temperature rises, so that, on the assumption that the quantum efficiency of reaction (1) is independent of the temperature, there are fewer activated molecules remaining at the higher temperatures to revert to *trans*-(I) with fluorescence emission. It follows from this that the fluorescence should diminish as the temperature is raised, a conclusion which is confirmed by experiment. Temperature-quenching also occurs at very low concentrations, at which dimerisation is negligible, showing that the probability of activated *trans*-(I) molecules changing to *cis*-(I) increases considerably as the temperature rises, while the mean life of the activated molecules so far as fluorescence-emission is concerned probably remains substantially constant.

The fluorescence phenomena which *trans*-(I) exhibits are too complex for satisfactory analysis by the crude methods available. The fluorescence band is broad, and stretches, apparently continuously, over roughly half the visible spectrum. At low concentrations the visual effect, without filters, is essentially blue, but as the concentration increases the band moves further into the longer wave-lengths, the visual effect changing through green-blue and blue-green to green. Viewed through appropriate filters, the maximum blue fluorescence occurs at about 0·1% (isethionate) and fades out completely at 10%; the yellow-green fluorescence is maximum at about 2% and extends through, with decreasing intensity, to both the highest (38%) and the lowest (0·01%) concentration examined. The existence of a maximum in the overall fluorescent effect is thus quite definite. The general effects of heating are to displace the band towards the shorter wave-lengths, and to cause a substantial decrease in the total fluorescence. Cooling produces the opposite effects. The fluorescence phenomena are not affected by exclusion of oxygen, and the temperature effects are reversible. At all concentrations greater than 0·1% the fluorescence, with vertical irradiation, is confined to the meniscus, showing absorption of the exciting radiation in a thin surface layer. As concentration is reduced below 0·1% penetration into the body of the solution increases.

Examination through light filters of standard spots of *trans*-(I) on filter paper, as used in the fluorescence-adsorption estimation, shows the presence of green and yellow in the fluorescence spectrum irrespective of concentration even down to 0·05 mg. per 100 c.c. Compound *trans*-(I) produced on dry filter-paper from *cis*-(I) or dimer by irradiation of dried spots of the solutions gives exactly the same effect, as do also dry spots of *trans*-4-amino-4′-amidinostilbene.

The general trend of the dimer/*cis*-(I) ratio with concentration in the early stages of insolation of *trans*-(I) was apparent from the main insolation experiments. To obtain further data, with concentration the only variable factor, solutions (0·1; 0·2; 0·4%) of the hydrochloride were insolated for sufficient times to give 20% conversion. At these concentrations absorption of the light responsible for the photochemical action is virtually complete in a thin surface layer of the solution. In spite of this it was found that the times required for 23% conversion were 8, 12, and 17·5 mins. respectively, while the actual quantities of activated *trans*-(I) converted into *cis*-(I) and dimer [*cis*-(I) plus dimer/2] in equal times (12 mins.) were as 5 : 6 : 7, showing that the quantum efficiency of dimer plus *cis*-(I) production increases with concentration. This is doubtless associated with the observed concentration-quenching of the fluorescence.

The initial rates of formation of dimer and *cis*-(I) may be expressed by the equations

$$d[D]/dt = k'[T^*][T] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

and

$$d[C]/dt = k''[T^*] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

from which the ratio, R, of the initial rate of formation of dimer to that of *cis*-(I) is given by the equation

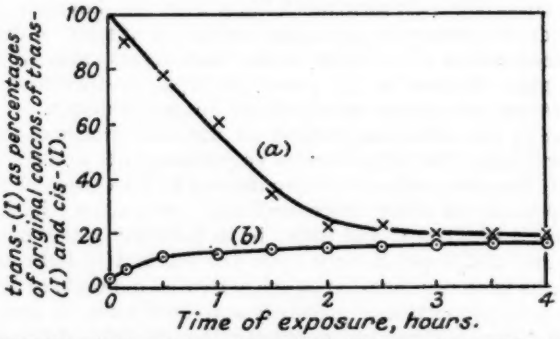
$$R = (d[D]/dt)/(d[C]/dt) = k'[T^*][T]/k''[T^*] = K[T] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (c)$$

The value of the ratio $R_2/R_1$ for initial concentrations $T_2$ and $T_1$ ($T_2$ the higher; other conditions constant) is given by

$$R_2/R_1 = T_2/T_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (d)$$

In practice, with the concentrations used (0·1—0·4%), it was not easy to determine the slopes of the tangents to the dimer and *cis*-(I) curves at the origin, and it was necessary to use experimental ratios determined at

FIG. 3.




*Exposure of* 0·02% *solution of* trans-(I) *and* cis-(I) *to north-sky light. Temp.*, 36°.
(*a*) = trans-(I) *remaining in the solution of* trans-(I).
(*b*) = trans-(I) *produced in the solution of* cis-(I).

about 20% conversion of the *trans*-(I). The ratio, R′, so determined, is lower than the true ratio, R, at the origin (cf. Fig. 1), and divergence increases as the initial concentration falls. The ratio $R'_2/R'_1$ was found to be greater than the ratio $T_2/T_1$ by a factor of 1·3—1·4. In view of the experimental difficulties the results obtained may be considered as offering strong support for the dimerisation theory.

The slow rate of dimerisation following the establishment of the equilibrium between *cis*-(I) and *trans*-(I) indicated that *cis*-(I) does not dimerise on insolation. On this assumption it was predicted that on insolation of a 1% solution of *cis*-(I) hydrochloride the *trans*-(I) concentration would rapidly rise to a maximum of about 18% of the original *cis*-(I) concentration and would then fall slowly so as to maintain the *cis*-(I)/*trans*-(I) ratio constant at 4—5. The rate of formation of dimer [from *trans*-(I)] would initially be *nil*, would rise to a maximum coinciding in time with the maximum of the *trans*-(I) curve, and would then decrease somewhat. The dimer–time curve would therefore show a point of inflexion. In spite of some interference from impurities in the *cis*-(I) hydrochloride used, the predicted features were reproduced almost exactly (cf. Fig. 4). Failure of the apparent *trans*-(I) to show a subsequent fall is attributed to interference by the secondary irradiation product responsible for the appearance of the yellow colour (q.v.). That the true concentration of *trans*-(I) does subsequently decrease follows from the existence of the point of inflexion in the dimer curve.

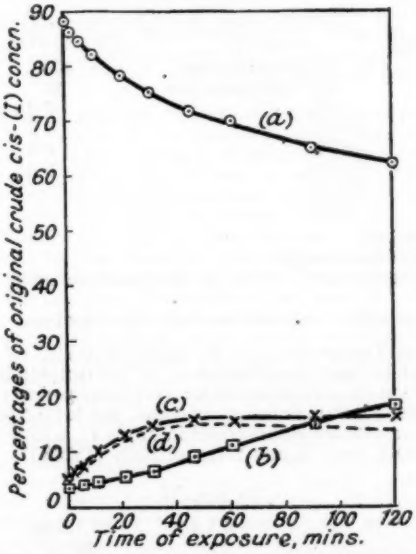
The photo-dimerisation mechanism of concentration-quenching may be of more frequent occurrence than is at present suspected. According to Weiss (*Trans. Faraday Soc.*, 1939, **35**, 37) all organic molecules which fluoresce strongly have fully conjugated bond systems. They are therefore potentially capable of dimerisation, If reversal of dimerisation is effected by radiation of similar frequency to that which produces dimerisation. and if equilibrium is largely in favour of the monomer, dimerisation might easily escape detection. The effect upon fluorescence of photo-dimerisation must be distinguished from that due to the formation of associated molecules in concentrated solution (*e.g.*, of many dyestuffs), which has already occurred before irradiation.

The proof that (III) has adsorptive powers comparable with those of *trans*-(I) is of importance as indicating a high degree of adsorption and retention in the body, as has been found in the case of *trans*-(I) (Henry and

Grindley, *loc. cit.*; Kirk and Henry, *loc. cit.*) and as indicating a possible cause of the delayed toxic effects produced by the dimer in human beings (Kirk and Henry, *loc. cit.*). Determination of the rate of excretion of (III) after intravenous injection will be investigated by the fluorescence-adsorption technique as soon as opportunity permits.

That *trans*-(I), both in solution and in the solid state, tends to develop a yellow colour on irradiation, the cause of which has not so far been explained, has been observed by previous workers (Fulton and Yorke, *loc. cit.*; Barber, *et al.*, *loc. cit.*; Kirk and Henry, *loc. cit.*). Kirk and Henry thought that it was due in part to the formation of *cis*-(I), but *cis*-(I) is colourless (Slack, private communication), and it has been observed that most of the acquired yellow colour is carried down along with *trans*-(I) sulphate. Solid *trans*-(I) hydrochloride and isethionate are both very slightly yellow, and concentrated solutions are strongly coloured. The natural yellow colour of a 1% solution of *trans*-(I) hydrochloride is weak, but on insolation the colour of the solution steadily increases and continues to do so after the main photochemical reaction is complete and the *cis*-(I)–*trans*-(I) equilibrium established. A concentrated (15%) solution of the isethionate is strongly coloured. On insolation the colour steadily diminishes until, at completion of the main photo-chemical change, it is only about 20% of the original colour, while 40% solutions become nearly colourless after full insolation. Crude

FIG. 4.




*Insolation of* 1% *solution of crude* cis-(I) *hydrochloride. Solutions* (23 c.c.) *contained in "Pyrex" flasks,* 50 *c.c. capacity. Temp.,* 45°.

(*a*) = cis-(I) *remaining.* (*c*) = trans-(I) *produced (expt.).*
(*b*) = *dimer produced.* (*d*) = trans-(I) *corrected for yellow irradiation product.*

*cis*-(I) hydrochloride prepared from insolated *trans*-(I) hydrochloride is invariably coloured. On insolation in solution (1%) a definite increase in the intensity of colour ensues, while insolation of the solid results in rapid yellowing. It appears, therefore, that there is a close connection between the yellowing on irradiation and the presence of *cis*-(I), suggesting that the yellow colour is due to a product of the further photochemical change of *cis*-(I). The colour is destroyed on bromination, from which it is concluded that the compound responsible for it is bromine-absorbing. Whether the absorption of bromine is due to addition at an ethylenic linkage or to substitution has not been ascertained.

The difference in behaviour on irradiation of *trans*-dimethyl-(I) as compared with that of *trans*-(I) and *trans*-monomethyl-(I) is of considerable interest. In absence of any chemical investigation of the photochemical instability of the mono- and the di-methyl derivatives it may be assumed that the former undergoes dimerisation and *cis–trans* isomerisation similar to *trans*-(I), while the latter is either substantially unchanged, or undergoes *cis–trans* isomerisation only. Fulton (*loc. cit.*) attributed the difference in behaviour to absence of a reactive hydrogen atom in the dimethyl derivative, while Henry (*Nature*, 1943, **152**, 690) suggested steric hindrance as being the cause. Whatever is the true explanation of the difference it is of interest to observe that the behaviour of these compounds on irradiation is closely similar to that of anthracene and its mono-*meso*-substituted derivatives on the one hand, which dimerise on irradiation, and its di-*meso*-substituted derivatives on the other hand, which are unaffected by irradiation (Bergmann, *Trans. Faraday Soc.*, 1939, **35**, 1052). Also of interest is the close parallel between the behaviour on insolation of *trans*-(I) and of the cinnamic acids, which likewise undergo *cis–trans* isomerisation and dimerisation on insolation, and reversal of dimerisation under the action of the short ultra-violet waves.

## Experimental.

*Main Insolation Experiments.*—Direct tropical sunlight between 11·30 and 13·30 hours, during which period its intensity remains fairly constant, was used, and, where necessary, experiments could be carried over from day to day since the photochemical changes cease when irradiation is discontinued. The solutions, freshly prepared in artificial light, were contained in "Pyrex" flasks which were tied, lying flat, on a board suitably holed and fitted with a perpendicular rod which was kept always pointing direct into the sun. In this way normal incidence of the sunlight was maintained, and the board was kept gently shaken so that during any one experiment all solutions were subjected to similar conditions of exposure, and of mixing. Most solutions were warmed to 42—45° before exposure so as to maintain a nearly constant temperature throughout the insolation period.

After exposure the total bromine absorption was determined on one aliquot, giving *cis*-(I) plus *trans*-(I) and dimer by difference from 100%, and a second aliquot was warmed to 60°, excess of sodium sulphate solution added dropwise to precipitate *trans*-(I) as the sulphate, the solution cooled overnight, filtered through sintered glass, and the bromine absorption of an aliquot of the filtrate determined to give the *cis*-(I). The bromination technique previously described (Henry, *J.*, 1945, 870; *Analyst*, 1945, **70**, 259) was used, the almost complete precipitation of the *trans*-(I) and the presence of *cis*-(I) being confirmed by spotting-out the *cis*-(I) filtrate on filter-paper and examining it in ultra-violet light (cf. Henry, *J.*, 1945, 870). Simultaneous precipitation of much of the dimer sulphate assisted by tending to carry down the *trans*-(I) sulphate. The conditions used were not such as to precipitate any *cis*-(I) sulphate. The *trans*-(I) used was free from *cis*-(I), but a small correction to all results was necessary to allow for unprecipitated *trans*-(I) [blank *cis*-(I) estimation at zero time]. The results of these experiments are summarised in Table I, and parts are illustrated in Figs. 1 and 2.

Table I.

| Expt. | Initial temp. | Initial concn. of *trans*-(I). | Dimer/*cis*-(I) ratio at early stage. | Final equilibrium *cis*-(I)/*trans*-(I) ratio. |
|---|---|---|---|---|
| I | 45° | 15% isethionate | 400 | 1·8 |
| II | 45 | 2% hydrochloride | 28 | 1·4 * |
| III | 28 † | 1% ,, | 7·3 | 4·6 |
| IV | 48 | 0·2% ,, | 0·5 | 4·0 |
| V | 28 † | 0·2% ,, | 0·9 | 4·6 |
| VI | 45 | 0·02% ,, | 0·05 | 4·7 ‖ |
| VII A ‡ | 42 | 0·1% ,, | — | 5·0 |
| VII B ‡ | 18 | 0·1% ,, | — | 4·4 |

* Equilibrium had not been established.

† Temperature rose to *ca.* 45° in the later stages.

‡ These results show the comparatively small effect of temperature upon the final equilibrium (photochemical) *cis*-(I)/*trans*-(I) ratio.

‖ Obtained by bromometric analysis after concentration and fractionation.

*Dependence of Dimer*/Cis-(I) *Ratio on Temperature.*—Two solutions (0·2%) of *trans*-(I) hydrochloride were insolated for 15 minutes, one being maintained at 19° and the other at *ca.* 64° by running hot and cold water respectively over the flasks. There was occasional interruption of the insolation for very brief periods in the high temperature flask, allowing for which it may be assumed that, other conditions being constant, the total *trans*-(I) changed into *cis*-(I) and dimer is independent of the temperature. The results are summarised in Table II, which includes comparable results for average temperatures of 33° and 48° derived from Expts. IV and V respectively (Table I).

Table II.

| Date | 6.1.45 | 23.12.44 | 26.12.44 | 6.1.45 |
|---|---|---|---|---|
| Approx. temperature | 19° | 33° | 48° | 64° |
| *Cis*-(I), C (%) | 8·9 | 17·7 | 17·5 | 17·1 |
| Dimer, D (%) | 16·9 | 16·5 | 9·5 | 6·7 |
| *Trans*-(I), T (%) | 74·2 | 65·8 | 73·0 | 76·2 |
| *Cis*-(I) plus dimer (%) | 25·8 | 34·2 | 27·0 | 23·8 |
| Ratio dimer/*cis*-(I) | 1·90 | 0·93 | 0·54 | 0·39 |
| C/(C + D) | 0·34 | 0·52 | 0·65 | 0·72 |
| D/(C + D) | 0·66 | 0·48 | 0·35 | 0·28 |
| (C + D/2)/(C + D) | 0·67 | 0·76 | 0·83 | 0·86 |

*Preparation of Crude* Cis-(I) *Hydrochloride.*—A solution of *trans*-(I) hydrochloride (4 g. in 20 l.) was fully insolated at 45° and then evaporated, finally to dryness, in the dark at 35°. The residue was treated with water (5 c.c.) at 35° and filtered to remove undissolved *trans*-(I) hydrochloride, and the filtrate was allowed to evaporate to dryness. Bromometric analysis of crude *cis*-(I) hydrochloride so obtained (3·51 g.) showed it to contain, as hydrated hydrochlorides: *cis*-(I), 88·4; *trans*-(I), 4·5; dimer, 4·0; free $H_2O$, 3·0%. The recovered products of the insolation of the original *trans*-(I) hydrochloride were: *cis*-(I), 3·10 g.; *trans*-(I), 0·66 g.; dimer, 0·14 g.; giving 4·7 for the *cis*-(I)/*trans*-(I) equilibrium ratio for 0·02% solution, and 0·045 for the dimer/*cis*-(I) ratio.

*Reversibility of* Cis-(I)–Trans-(I) *Change.*—(i) Solutions (0·02%) of *cis*-(I) hydrochloride, prepared as above, and *trans*-(I) hydrochloride were exposed simultaneously under identical conditions (temp. 36°) to bright north-sky light, and the *trans*-(I) estimated in each solution at suitable intervals by the fluorescence-adsorption method. The results are given in Fig. 3, and show that the same equilibrium mixture arises from both *cis*-(I) and *trans*-(I). The *cis*-(I)/*trans*-(I) equilibrium ratio given by this method was 4·4.

(ii) A solution of *cis*-(I) hydrochloride (0·5 g. in 2·5 l.), prepared as above, was fully insolated and the solution evaporated, finally to dryness, in the dark at 35°. The residue was treated with water (1 c.c.) at 35° to remove most of the *cis*-(I). The undissolved material, on fractionation, yielded 0·04 g. (8%) of crystals which were shown to be *trans*-(I) hydrochloride (composition, fluorescence and adsorption, behaviour on insolation, bromine absorption, and insolubility of sulphate).

*Evidence for Polymerisation.*—The saturated irradiation product can be isolated as the sulphate in reasonably pure condition by addition of sodium sulphate to the slightly acid solution and recrystallisation from hot, slightly acidified, water, the acidity being necessary to prevent hydrolysis of the amidino-groups. The purest product obtained gave: N, 12·9; $SO_4$, 22·2; loss at 110°, 13·3; loss at 200°, 15·8. Calc. for $C_{32}H_{32}N_8.2H_2SO_4.8H_2O$ (III): N, 12·8; $SO_4$, 22·1; $H_2O$, 16·6. Calc. for $C_{16}H_{16}ON_4.H_2SO_4.3H_2O$ (II): N, 12·8; $SO_4$, 22·1; $H_2O$, 12·4%. Decision between the

two formulæ depended, therefore, entirely upon the content of water of crystallisation. As the sulphate does not dehydrate readily, even on prolonged heating at 110°, it was obviously unsuitable for deciding between the two alternatives owing to the possibility of other changes occurring.

The oxalate of the irradiation product is comparatively insoluble, and dehydrates at room temperature over sulphuric acid. It is, however, difficult to purify, as it does not readily redissolve in hot water and will not crystallise from a slightly acid medium. Results obtained with oxalate of doubtful purity were intermediate between the requirements of (II) and (III); the conclusions were therefore indefinite, and efforts along these lines were discontinued.

The results of the kinetic experiments showed that, at the very high concentrations (40%) which can be obtained with *trans*-(I) isethionate, negligible proportions of *cis*-(I) and *trans*-(I) would remain in the solution fully insolated at low temperature, thus avoiding the need for purification. *Trans*-(I) isethionate readily dehydrates over sulphuric acid at 35° (Found for material so dried: N, 10·65; S, 12·15; bromine absorption, 309 mg./g. Calc. for $C_{16}H_{16}N_4,2HO{\cdot}C_2H_4{\cdot}SO_3H$: N, 10·85; S, 12·40%; bromine absorption, 310 mg./g.), suffers no further loss at 110° (24 hours) and only slight loss (0·05% per hour) at 200°. In spite of the rather low figures for N and S the salt, dried to constant weight over sulphuric acid at 35°, may safely be assumed to be anhydrous. The isethionate of the irradiation product is extremely soluble and does not crystallise; instead, on evaporation the solution finally sets to a glassy solid which, over sulphuric acid at 35°, dries out until the weight reverts to the original weight of anhydrous *trans*-(I) isethionate. This has been repeated several times with the same result, and disproves carbinol (II) formation and shows polymerisation of internal rearrangement. In one experiment *trans*-(I) isethionate (1·5893 g.) dried over sulphuric acid at 35° to 1·5612 g. Water (3 c.c.) was then added and the solution insolated for 8 hours at 10°. On evaporation (35°) and subsequent drying, in the dark, over sulphuric acid at 35° the weight became constant, after 13 days, at 1·5613 g. The dehydration curve was quite smooth. The final product, dissolved and made up to 100 c.c. for analysis (solution *A*), contained 0·45% of *trans*-(I) and 0·25% of *cis*-(I) giving a *cis*-(I)/*trans*-(I) ratio of 0·6, and 99·3% conversion of the original *trans*-(I) to dimer.

On insolation, or irradiation with filtered light from the mercury lamp, of solution *A* (equivalent to 1·1% dimer hydrochloride) the concentration of *trans*-(I) decreased from 4·5 to 1·7 mg./100 c.c. and that of *cis*-(I) increased from 2·5 to 5 mg./100 c.c., to give a *cis*-(I)/*trans*-(I) ratio of 3. Other similarly prepared solutions gave ratios of 4 and 5 after irradiation.

*Reversal of Dimerisation.*—(i) *Reversal in solution.* Solution *A* underwent no detectable change on irradiation (45 minutes) with the filtered (3000—4000 A.) light of the mercury lamp, other than the *trans*-(I)–*cis*-(I) readjustment described. On irradiation with the unfiltered light of the lamp there was a marked, and steady, increase in the concentration of both *trans*-(I) and *cis*-(I) in the solution, particularly evident on examining a spot of the solution on filter-paper, but less so on examining the fluorescence of the bulk solution on account of concentration-quenching. Using the fluorescence-adsorption method the concentration of *trans*-(I) increased steadily from 4 mg./100 c.c. at zero time to 66 mg./100 c.c. after 115 minutes, at which time equilibrium had still not been reached. Bromometric analysis of the solution at this stage showed that, of the original dimer, 6·8% had been converted to *trans*-(I) and 15·3% to *cis*-(I), giving a *cis*-(I)/*trans*-(I) ratio of 2·2. On repeating with a 0·1% solution (250 c.c.) of dimer, irradiation being continued for two hours after equilibrium as determined by the fluorescence-adsorption method had been reached, bromometric analysis of the solution gave: *cis*-(I), 65; *trans*-(I), 21; dimer, 14%; *cis*-(I)/*trans*-(I), 3·1; dimer/*cis*-(I), 0·22. The higher value of the *cis*-(I)/*trans*-(I) ratio found in this experiment suggests that reversal of dimerisation produces *trans*-(I) only, which is then partially converted into *cis*-(I); but conditions were too complex, and data too scanty, for a decision on this point to be possible at present. The dimer/*cis*-(I) ratio is what would be expected for the concentration used.

(ii) *Reversal on dry filter-paper.* A drop (Oreyer pipette) of dimer solution, spotted out on filter-paper and dried, shows, in filtered ultra-violet light, only the fluorescence due to the small quantities of *trans*-(I) and *cis*-(I) present. On insolation (1 hour) some development of fluorescence in the empty outer zone of the spot is detectable, but the effect is small. On very brief exposure to the unfiltered light of the mercury lamp and subsequent examination in the filtered light, a brilliant fluorescent spot is observed, the area of which is dependent upon the concentration of the dimer solution used. Maximum development of fluorescence occurs within 1 second. With a 1% solution of dimer the fluorescence which develops covers practically the whole area wetted by the drop, but as concentration is reduced the radius of the fluorescent area diminishes (showing strong adsorption of the dimer) until, at the low concentrations which would be encountered in the excretion of the injected compound, the fluorescent effect is an annulus exactly similar in appearance to that given by *trans*-(I) (cf. Henry and Grindley, *loc. cit.*). Spots of dimer solution (0·1—10 mg./100 c.c., as hydrochloride) on filter-paper showed no fluorescence below 0·5 mg./100 c.c., while the 10 mg./100 c.c. spot showed 0·1 mg./100 c.c. against *trans*-(I) standards. After brief exposure to the unfiltered light of the mercury lamp the fluorescence of the spots, on comparison with *trans*-(I) standards, gave 0·05—5·0 mg./100 c.c. of *trans*-(I). At each concentration the developed fluorescence was that of *trans*-(I) at half the concentration. By comparison, after development, of a spot of an unknown dimer solution in water or the biological fluids with a series of standard spots similarly prepared (washed if necessary) and developed, there is no doubt that satisfactory estimation of the unknown could be effected and, for example, rate of excretion after injection determined.

(iii) *Wave-band producing reversal of dimerisation.* The rate of development of the fluorescence of spots of dimer solution (50 mg./100 c.c.) on filter-paper on exposure to the full light of the mercury lamp passed through various filters (water, dimer solution, and solutions of lead acetate, contained in a silica capsule giving 1 cm. depth of liquid) was used for this purpose. The dimer spot was placed beneath the capsule and irradiated for known periods with the full light of the lamp, and its fluorescence was then compared with a similar spot fully developed. With water there was immediate and full development; with dimer solution (1%) no significant development after 60 seconds' exposure; with lead acetate (1 : 25; 2700 A.) approximately 50% development after 60 seconds exposure; with lead acetate (1 : 300; 2500 A.), full development after 30 seconds' exposure; with lead acetate (1 : 1500; 2400 A.), full development after 15 seconds' exposure. The maximum of the absorption band of an irradiated solution (1%) of *trans*-(I) was found by Goodwin (*loc. cit.*) to be at 2510 A.

*Adsorptivities of* Trans-(I), Cis-(I), *and Dimer.*—Using the technique of Henry and Grindley (*loc. cit.*) three spots of each solution (50 mg./100 c.c.) were prepared by transferring 0·1 c.c. to filter-paper. One spot of each solution was left unwashed, one of each washed radially with water (0·2 c.c.), and one of each washed radially with N/10-hydrochloric acid (0·2 c.c.). After drying the *cis*-(I) spots were developed in filtered ultra-violet light, and the dimer spots in unfiltered light of the mercury lamp. The fluorescences of corresponding spots of the compounds were then compared. The unwashed spots and those washed with water showed no significant differences in fluorescent areas, but washing with acid caused much more washing out of *cis*-(I) and dimer, which were similar, than of *trans*-(I). The adsorptivity of the dimer (filter-paper) is therefore rather less than that of *trans*-(I) and comparable with that of *cis*-(I).

*Variation of Dimer*/Cis-(I) *Ratio with Concentration.*—Solutions (200 cc.; 0·1; 0·2, 0·4%) of *trans*-(I) hydrochloride were insolated at 43°, for 9, 12, and 15 minutes respectively, and the solutions analysed bromometrically. The results are given in Table III, from which it is calculated on a proportionality basis that 23% total conversion of the original *trans*-(I) would have occurred in 8, 12, and 17·5 minutes respectively, and that in equal times (12 minutes), the actual quantities of activated *trans*-(I) converted into *cis*-(I) and dimer would have been as 5 : 6 : 7.

TABLE III.

| | | | |
|---|---|---|---|
| Init. concn. of *trans*-(I)HCl, g./100 c.c. | 0·1 | 0·2 | 0·4 |
| Time of insolation, min. | 9 | 12 | 15 |
| *Cis*-(I) formed, % of original | 20·8 | 14·0 | 7·1 |
| Dimer formed, % of original | 5·1 | 9·0 | 12·8 |
| Total *trans*-(I) changed, % | 25·9 | 23·0 | 19·9 |
| Time for 23% change, mins. | 8 | 12 | 17·5 |
| *Cis*-(I) plus dimer/2, % | 23·4 | 18·5 | 13·5 |
| Dimer/*cis*-(I) ratio, R′ | 0·245 | 0·64 | 1·80 |
| R′0·2/R′0·1 | 2·6 (= 2 × 1·3) | | |
| R′0·4/R′0·2 | | 2·8 (= 2 × 1·4) | |

*Insolation of* Cis-(I) *Hydrochloride Solution* (1%).—The experiment was carried out, with material prepared as described above, as for *trans*-(I) solutions, each flask (capacity 50 c.c.) containing 23 c.c. of the solution, heated to 45° immediately before insolation. After exposure the solutions were analysed bromometrically in the usual way. In carrying out the analysis of these solutions it was observed that there appeared to be some lag in the completion of the bromine-absorption, in consequence of which the period of contact with the bromine was increased, for all estimations, from the usual 2—3 minutes to 10 minutes. The lag is attributed to rather slow absorption of bromine by the yellow irradiation product, which was present in small quantity in the original *cis*-(I) preparation and further increased during insolation of the solution, and not to bromination of *cis*-(I) taking place more slowly than that of *trans*-(I), though this possibility has not been ruled out. That the yellow compound does absorb bromine is indicated by the fact that bromination of the yellow solution by addition of excess of freshly prepared bromine water (removing the excess by a current of air) destroys the yellow colour.

The results of the insolation of the *cis*-(I) hydrochloride solution are shown graphically in Fig. 4. Failure of the *trans*-(I) concentration to show a decrease in the later stages is attributed to the presence of the yellow compound which, since it absorbs bromine (under the conditions used) and is largely precipitated together with *trans*-(I) sulphate, appears in the analysis as *trans*-(I). The observed *trans*-(I) concentration is, in fact, the true *trans*-(I) plus most of the yellow compound, which latter increases with the time of insolation. The true *trans*-(I) concentration should therefore be as represented by the dotted curve.

*Products of Hydrolysis of* Cis-(I), Trans-(I), *and the Saturated Insolation Product.*—Complete removal of the nitrogen could be effected, though with difficulty, by prolonged refluxing in the dark with aqueous-ethanolic sodium hydroxide until evolution of ammonia ceased. After removal of the ethanol the acids could be precipitated as amorphous or gelatinous solids by acidification of the diluted aqueous solutions. The compounds *cis*-(I) and *trans*-(I) produce *cis*- and *trans*-stilbene-4 : 4′-dicarboxylic acids respectively on hydrolysis. Assuming no rupture of the *cyclo*butane ring during hydrolysis, (III) would give 1 : 2 : 3 : 4-tetra-(4′-carboxyphenyl)*cyclo*butane (V); while (II) would give 1 : 2-di-(4′-carboxyphenyl)ethan-1-ol (VI).

The acid produced as above from the saturated insolation product [containing only small quantities of *cis*-(I) and *trans*-(I)] was redissolved in slight excess of sodium hydroxide, the solution largely diluted, and the acid reprecipitated by rapid addition, with stirring, of excess of hydrochloric acid to the hot solution. The acid was filtered off, washed with cold water, and air-dried to constant weight. The product was readily and completely soluble in ethanol, was nitrogen- and ash-free and had no m. p. up to 310° (Found: equiv., 141·4). Over concentrated sulphuric acid at 30° it readily dehydrated to constant weight (24 hours; 4·55% loss), and the dehydrated material recovered nearly the whole of the loss in weight on exposure to the air for two days [equiv. calc. for dehydrated material, 135. (V) requires 134; (VI) requires 143]. The acid is therefore assumed to be (V).

Crude specimens of *cis*-(IV) and *trans*-(IV) were also prepared, as above, from the corresponding amidines. Equal quantities (0·02 g.) of these, and of (V), were dissolved in a small excess of sodium hydroxide, neutralised, and the solutions diluted to 20 c.c. (100 mg. of acid/100 c.c.). These solutions were spotted-out on filter-paper in the usual way and the dry spots examined in the filtered light of the mercury lamp. The spot prepared from *trans*-(IV) gave a strong fluorescence immediately, and there was no change on further irradiation (10 minutes). That prepared from *cis*-(IV) showed only a faint fluorescence at first, due to the presence of a little *trans*-(I), but during exposure fluorescence steadily developed over the whole area wetted by the drop, exactly as had previously been found for *cis*-(I). The spot prepared from (V) showed no initial fluorescence, and no fluorescence had developed after irradiation (10 minutes) with the filtered light. On irradiation of this spot with unfiltered light of the lamp fluorescence developed over the whole area of the spot until it was comparable in intensity with that of the *cis*-(IV) spot fully developed. Exposure for about 1 minute was required for maximum fluorescence to be reached, as compared with about one second in the case of a similar spot of (III). It is evident, therefore, that (V) is also unstable under the action of the short ultra-violet waves and reverts to *trans*-(IV).

The solutions of the sodium salts of *cis*-(IV), *trans*-(IV), and (V) were insolated (15 minutes), with shaking, and again spotted out. The spot from (V) showed no initial fluorescence and no fluorescence developed on exposure, showing that the compound is stable to sunlight. The spots prepared from *cis*-(IV) and *trans*-(IV) after insolation each had the same initial fluorescence, much less than that of uninsolated *trans*-(IV) solution, and on exposure extensive fluorescence due to *cis*-(IV) developed to the same extent in each. It is evident, therefore, that on insolation *cis*-(IV) and *trans*-(IV) undergo *cis-trans*-isomerisation until equilibrium between the two forms is established.

The fluorescence of the *trans*-(IV) spot was only 5—10% of that of a *trans*-(I) spot at the same equivalent concentration, showing the depressing effect on fluorescence of replacement of the amidino-groups by carboxyl groups.

The mercury lamp used throughout this work was provided with a white glass filter transmitting little light outside the range 3000—4000 A. (suppliers' description). For concentration- and temperature-quenching observations the solutions were contained in open test-tubes mounted so that all could be irradiated, heated (oven) or cooled simultaneously. To exclude oxygen the solutions were oven-heated (110°; 1 hour) and a layer of toluene was added while hot.

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WELLCOME CHEMICAL LABORATORIES,
SUDAN MEDICAL SERVICE, KHARTOUM.

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# OBITUARY NOTICE.

## WILLIAM ARTHUR BONE.*

**1871—1938**

WILLIAM ARTHUR BONE, the distinguished fuel technologist and chemist, was essentially a product of heredity and environment. His character, work, politics, friendships and religion were all in the nature of loyalties to his ancestry and upbringing and indissolubly intertwined, so that his evolution as a man and as a scientist bears the aspect of inevitability.

By birth and upbringing, Bone was a north countryman and inherited the pride of his race. He was born at Stockton-on-Tees in 1871, the eldest child of Christopher and Mary Elizabeth Bone, both of whom appear to have handed on to their son a goodly heritage. Christopher Bone was a tea merchant and a prominent citizen of the town, taking an active part in its social and political welfare, and being generally respected for his forcefulness, sincerity, fearlessness and independence of thought, speech, and action. He was public-spirited to a degree, a born fighter for what he considered right and just, who, despite a magnificent physique, overtaxed his strength and died early. Mary Elizabeth Bone, to whom indirectly, as will presently be seen, William Arthur owed his choice of career, was of an equally lively intelligence and nature and shared her husband's interests. Both were ardent Liberals and whole-hearted Wesleyans. We can trace nothing negative in their mental make-up. Looking still further back into the family history to the respective parents of Christopher and Mary Elizabeth, one finds the same reality of outlook and lively interest in and feeling for life. It was this characteristic of positiveness that, handed down in generous measure to their grandson, was the dominating contribution to his greatness. In an age when mental and moral structure is rarely uncorroded by fear in one or other of its many manifestations, the positive personality must make enemies. In compensation therefor, however, the friends he attracts are unusually staunch and true, and respect is almost universal. Bone had firm friends in all classes and walks of life; indeed, his avoidance of class distinctions amounted almost to genius. Amongst his opponents, scientific and otherwise, he paradoxically numbered many friends, and there were few who did not admire the courage of his convictions. Thus he took an active part in the local St. Albans politics against Sir Francis Freemantle. To an expression of regret at the death of one of his chief constituents and opponents, Sir Francis added that he had learnt greatly to respect Bone's criticism and views.

Bone was educated at Middlesbrough High School, then at the Quakers' School at Ackworth, where the headmaster, one Frederick Andrews, became, according to Bone himself, one of the abiding influences of his early school days. From Ackworth he went to Stockton High School, which was fortunate enough to possess as science master a man of outstanding personality, " a genius in his power of realistic description," to quote Bone's own words. To the inspiration of this teacher the pupil avowedly owed a deep debt of gratitude. It should be mentioned here that Bone had early decided upon a scientific career. This was in the maternal tradition, for his mother's brother, the late T. C. Hutchinson, was manager and part owner of the Skinningrove Iron Works, and amongst the blast furnaces young Bone was wont to spend most of his spare time. Leaving Stockton High School, he passed a year at the Leys School, Cambridge, proceeding as a student to Manchester University, where the two outstanding personal influences were Theodore Nield and H. B. Dixon.

During all these early years Bone had the inestimable advantage of a very happy home life and understanding parents for whom he entertained the greatest affection. He was healthy and robust and took an active part in school and college games and sports. In addition he was fond of music and joined in amateur operatics. He played both organ and piano and attended concerts in Manchester. He liked the theatre, debating societies, and politics, and was genuinely interested in religious questions. The family traits had appeared in full force. All the essentials were already there. Time, the power to recognize opportunity and the courage to seize it with both hands, were all that were needed to effect the expansion to a rare breadth and completeness of character and achievement

The thoughts and activities of a dominant personality are rarely incongruous. Bone's career as a scientist and citizen, therefore, pursues a direct logical course. In 1892, having won a scholarship, he left Manchester and studied for a year in Heidelberg; a fruitful interlude which gave him a command of German, whetted an inherent taste for travel, and broadened his scientific outlook. On his return, he became officially engaged to and later married Miss Kate Hind, the daughter of a prominent citizen, twice mayor of Stockton. This was another manifestation of his incontrovertible loyalty to his breed; he had known Kate Hind as a boy and had very early marked her down as his future wife. The two families shared very much the same outlook and had the same social background. It follows that Mrs. Bone was broad-minded and intelligent, musical and artistic, hospitable and domesticated. Though untrained, she was greatly interested in his scientific work and shared his love of entertaining his scientific friends and students. After the marriage Bone left Manchester to join the staff of the Battersea Polytechnic, but London did not agree with Mrs. Bone's health, and he himself hankered after broader spheres. 1898 saw him once more in Manchester in the laboratory of H. B. Dixon.

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Followed several very busy years. The arrival of three children, first a daughter, then a son, and then another daughter, was a compelling incentive to extra endeavour in his work, for though his general tastes were simple, he regarded really adequate holidays as a necessity rather than an extravagance and considered them well worth the additional hours put into correcting examination papers. His clan complex appears to have been very definitely developed for, not content with having his own immediate family with him on the long annual summer vacation, he would take also his mother, his sisters-in-law, and his aunts. Later, his friends and acquaintances and students would share his time and hospitality at what was almost his second home. In the old manor farmhouse at Burnsall he would entertain his guests, introducing them to one of his dearest delights, the joy of long walks amid the beauties of his beloved Yorkshire dales.

In 1905 he was appointed first Livesey Professor at the University of Leeds. From this period date many of his most important researches, the fame of which took him to America on a highly successful lecture tour. In this connexion fate played him two of her contradictory tricks. Berths had been booked for him and a companion on the " Titanic." At the last moment the companion fell ill and the passages were cancelled. Bone used to tell of the complexity of his feelings when, over a cup of tea in a café in Leeds, he heard the newsboys cry out the news of the disaster to the ill-fated ship. Fate saved him from this catastrophe, however, almost to overwhelm him in another. The postponed lecture tour successfully accomplished, he was taken ill on the return voyage with ptomaine poisoning and all but died.

1912 saw his next and last move back to London. It was then that I first met him at an interview for the post of demonstrator. I was appointed and told to report for duty at 10 a.m. a month hence. I duly arrived, but knocked in vain at the door of Bone's room. I knew no one in the Imperial College, except a fellow student from Zürich and M. O. Forster. I called on them and returned at 11 a.m. Still no reply, so I set off to explore the Royal College of Science. Noon saw me once more approaching Bone's door which suddenly opened, disclosing the great man himself. Seeing me, he demanded, " And who may you be? "—only his actual words were rather more forceful! My explanation drew forth the angry challenge, " Didn't I tell you to be here at 10 o'clock? " On my riposting that I had been there not only at 10 but also at 11, and now at 12 o'clock did not like the peculiar warmth of his welcome, he laughed in high good humour, led me into his room and soothed my rather ruffled feelings completely by saying " Thank heaven for somebody who will speak up for himself." All who knew Bone will recognize that this episode is completely in character. It began for me a lifelong friendship which not only stood the strain, but was indeed strengthened by many similar sword-crossings.

At the Imperial College, Bone had the most magnificent opportunity of his scientific career. To create something new is the born artist's real desire whether he be poet, painter, musician, or scientist, and into the creation of a new department of fuel technology at the Imperial College, South Kensington, Bone threw himself with whole-hearted vigour. Whither his urge for self-expression bore him the years have amply shown. Under his inspired leadership rose a research school of world-wide renown.

Meanwhile, the family decided to settle at St. Albans. His wife's health suffered in London, and the children's education had to be considered; in both these respects St. Albans filled the bill. Two short years afterwards, however, tragedy struck. While on holiday at Burnsall, his wife died after an operation. Broken down by his personal calamity, another calamity saved him. It was the summer of 1914. The declaration of the world war troubled him exceedingly for Bone was a pacifist. The ensuing mental conflict proved salutary, but even more so was his characteristic allegiance to the family. On the outbreak of war, his only brother chanced to be on a visit to Germany and was forthwith interned. Bone was left with the responsibility of looking after the prisoner's affairs and thus forced to occupy his mind with troubles other than his own. During 1914—18 he carried out various investigations and researches in chemical and fuel problems connected with the war, and also trained skilled chemists for munition factories and the like, but loyalty to his own ideals prevented him, it is said, from carrying out suggested investigations on the use of poison gases.

In 1916, Bone married Miss Mabel Isobel Liddeard, a clever and charming woman who was of great assistance to him in his work. She died in 1922. This second blow to his family happiness threw him back even more closely upon his work which he proceeded to attack with redoubled vigour. His department grew rapidly and flourished and, on his retirement in 1936, he had the pride and satisfaction of knowing that he had in turn passed on to others a worthy heritage.

Such is the bare outline of Bone's life and career. Two characteristics stand out crystal clear—his vigour and breadth. His scientific work echoes these two traits. The field he ploughed and furrowed, sowed and reaped was unusually wide.

Much of what Boswell said of Johnson is peculiarly applicable to Bone: " Man is in general made up of contradictory qualities. . . . In proportion to the native vigour of the mind the contradictory qualities will be the more prominent. . . . At different times he seemed a different man in some respects; not, however, in any great or essential article upon which he had fully employed his mind and settled principles of duty." The defects of Bone's qualities were often apparent and to lesser natures perhaps seemed to submerge them. He was self-willed and at times " irritable in his temper," but the Johnsonian parallel still holds good for " he was of a most humane and benevolent heart which showed itself not only in a most liberal charity but in a thousand instances of active benevolence." His religious outlook was modern. Brought up as a Wesleyan and coming early under Quaker influence, he retained an interest in both churches to the end. He professed no dogmatic or sectarian faith, however, but was satisfied to avow an undenominational and non-ecclesiastical

Christianity such as he believed to be expounded in the " Pilgrim's Progress "—a book on which he was an acknowledged authority and which he believed capable of a very liberal interpretation. His knowledge of the Bible astonished even those whose chief business is its study. He had a great respect for serious religious opinion of any creed, but could not and would not tolerate cant or hypocrisy or any form of religious persecution. His was the true religion of visiting the fatherless and the widow and had its expression in his many charitable works. He was an active member of the General Committee of the National Children's Homes and Orphanages and a generous donor to its funds. His sympathy for those in trouble inside and outside his own circle of relatives was practical, and he was always ready to obtain relief for scientific workers in distress. In dealing with such cases he took endless trouble to find help. Lonely people, especially old ladies and students from abroad who were friendless, won his ready sympathy and were warmly received into the family fold.

After the war, most of Bone's holidays were spent in travelling abroad or cruising. The homely enduring delights of Burnsall did not check the desire to see other places or blind him to the more flamboyant beauties of scenery on a grander scale. He holidayed in Canada and the West Indies, Palestine and the Mediterranean countries, Switzerland and Scandinavia, and went forth on all his journeyings mentally well prepared; for he was an inveterate reader and had " accumulated a vast and various collection of learning and knowledge which was so arranged in his mind as to be ever in readiness to be brought forth " and had a " certain continual power of seizing the useful substance of all that he knew and exhibiting it in a clear and forcible manner so that knowledge which we often see to be no better than lumber in men of dull understanding was, in him, true, evident and actual wisdom." His reading covered archaeology, geology, economics, history, and, strangely enough, he was an ardent student of military history. This predeliction, in complete contradiction with his views as a pacifist, was always a source of amusement to his children. He never missed a battleground in his travels with them, and one can see them listening, tongue in cheek, as their peace-loving father expounded with obvious glee and in great detail all the history of the campaign and the plan of battle. In retrospect, knowing how much he enjoyed a mental fight, the pacificism and not the military history seems the incongruity. He hated ecclesiastical show, pomp and ritual, but loved old churches and cathedrals and, like the ordinary sightseer, took them all in his stride. This was probably no real contradiction in tastes, but a staightforward inheritance from his maternal grandfather who was a great lover and collector of the old and beautiful, especially furniture, china and glass, all of which things are part of the treasure trove of historical and ancient churches.

One last link with Boswell who writes this of Johnson : " Though even awful of deportment, he possessed uncommon and peculiar powers of wit and humour." It is undeniable that Bone possessed the rare and godlike gift of inspiring " awe "—for Boswell uses the word in its true sense. It is also undeniable that Bone had a rare sense of humour. It illuminated the man, compensated for his sterner and less lovable qualities, and made of hours passed at his own fireside a vividly remembered joy. His fund of stories was inexhaustible, and he was a born narrator. In the North Country tradition, his stories were often told against himself. His native wit would out, even to his own disadvantage. On the occasion of being interviewed for a post, the interviewer was hostile, an attitude Bone was quick to sense. Questions became more and more personal until at last came, " What is your religion? " Swift and terse came the reply, " I'm damned if I know." The fact that this was probably true enhances rathers than detracts from the story, as the best humour always carries the sting of truth.

Something has been said in passing of his interest in politics. Another lasting interest should be mentioned. Bone was a keen cricketer. When he could no longer take part in the game himself, he was assiduous in his attendance at playing fields. During his last illness the Test Match was being fought. Only a few hours before he died, he was eagerly asking about individual players and how they stood in the game. He was very loyal to his interests and loves.

Looking back, perhaps the greatness of Bone's character was best shown by the way he faced his last eighteen months of illness. Whatever he felt inwardly, he never let any of his family see the slightest trace of fear or pessimism before each of his major operations. He always emphasized the most optimistic views of his medical advisers, although his critical mind would never have allowed him to do this with any other subject. It was a feat of mental control of which very few would be capable.

G. I. Finch.

## Scientific Activities.

Bone's scientific work had a singleness of purpose which makes it easy to view it as a whole. From the moment when his training was such as to enable him to become an investigator, till the time of his death, the whole of his energy was applied to investigate fuels and their combustion. He intended to be a master of his subject and he became one. Reviewing the work as a whole, and realizing that it was no doubt technical applications which supplied the impetus to it from his earliest years, a remarkable feature is that these applications did not in any way warp the plan of his work which was purely scientific; the other marked feature throughout was its thoroughness. There was nothing slipshod; infinite pains were taken. Thus the work sometimes appears ponderous, but is always marked by something new and something interesting. The pains he took were well rewarded in discovery. Practically all Bone's work was carried out along with col-

laborators, and they no doubt experienced his exaction, but all would agree that the training which his horror of slipshod work and the singleness of his purpose provided, was an invaluable experience.

Bone gave a summary of his work in a lecture before the Society of Chemical Industry at the time of his reception of the Medal of that Society in 1933, and the following quotations show the influences which started him on his career :

" I have selected ' Forty Years of Combustion Research ' as my theme, because of all chemical subjects, not only does it lie nearest my heart, but it raises issues of profoundest general interest to philosophers and technologists alike."

" Born and bred as I was on Teeside, amid the roar and smoke of iron-smelting, steel-furnaces, rolling mills, engineering works, and shipyards, where thousands of tons of coal were daily swallowed up and the night sky reddened with the blaze thereof, from childhood upwards I have ever been a fire-worshipper, and the older I grow the more fervent do I become."

" When, 45 years ago, I entered Owens College, Manchester, for a training in chemistry and physics, with the intention of subsequently joining the then new enterprise of my uncle, the late T. C. Hutchinson, at the Skinningrove Ironworks, I came under the magnetic influence of the late Prof. H. B. Dixon, and was thereby soon diverted from my original path into that of scientific investigation, without, however, losing my industrial interests. Hence I have been enabled to envisage combustion from both points of view."

H. B. Dixon unfolded in his lectures at Owens College, Manchester, the state of combustion chemistry as it then stood. When Bone went there in October 1888 it fired, as he said, " my imagination and threw the prospect of iron and steel making quite out of my mind." After graduating three years later, together with his friend and fellow student, Bevan Lean, he begged to be enrolled as one of Dixon's research students, and his first paper was published in 1892 along with Lean, and was entitled : " The Behaviour of Ethylene on Explosion with less than its Volume of Oxygen." Dixon suggested the investigation. Dalton, Kerston and others had found that ethylene burnt with its own volume of oxygen only produced carbon monoxide and hydrogen. It had been thought that in the combustion of a hydrocarbon the hydrogen was burnt preferentially, but Dalton's much-neglected experiments were against such a view. Lean and Bone's work confirmed these older observations and they further found that when the amount of oxygen was reduced small quantities of methane and acetylene were also formed.

The following paragraph from the same lecture, read in the light of the whole of Bone's work, shows how much Dixon's teaching influenced him :

" It was a rigorous school of research to which we were admitted, and its discipline was such as only strong minds could stand. As I have already said elsewhere, Dixon's singularly clear and penetrative mind referred everything to the final test of a well-ordered experiment, critically carried out without hurry or bias, and with the results checked at every point. He impressed upon all the paramount importance of accuracy and truth, together with the highest standard of experimental work. His method was to advance an experimental proof step by step, by a process of exclusion, until it had been narrowed down to a single issue, which finally had to be tested in every way. We were taught also to criticise our results, to eschew all rash speculation, and to limit ourselves to such explanations as were proven or provable."

The following scheme, summarizing the subjects of Bone's researches and the dates of publication, provides a key to the development of his work :

| | Period of publication. | | |
|---|---|---|---|
| | Early. | Middle. | Late. |
| Organic chemistry | 1893—1904 | — | — |
| Union of carbon and hydrogen | 1896—1901 | 1908—1910 | — |
| Slow combustion of hydrocarbons | — | 1902—1906 | 1932—1937 |
| Thermal decomposition of hydrocarbons | — | 1905—1914 | — |
| Explosive combustion of hydrocarbons | 1892—1897 | 1906 | 1934—1936 |
| Flame propagation | 1897 | — | 1927—1936 |
| Combustion of carbon monoxide | — | — | 1925—1930 |
| Catalytic combustion | — | 1906—1912 | 1925—1927 |
| Combustion at high pressures | — | 1906—1933 | |
| Chemistry of coal | — | — | 1919—1937 |
| Blast furnace reactions | — | — | 1926—1938 |

His work will reviewed in accordance with this scheme.

Bone left Manchester in 1896 for a while to study under Victor Meyer at Heidelberg. His natural abilities and excellent memory no doubt made the study of organic chemistry congenial to him and, in spite of Victor Meyer's interest in combustion, Bone worked on a problem of organic chemistry : " Indoxazen Derivatives." Returning to Owens College, Bone continued studies in organic chemistry and his next papers were published in the *Transactions of the Chemical Society*, along with W. H. Perkin, junr., who had recently been appointed to the Chair of Organic Chemistry. The investigations followed upon some work of Perkin's on the *cis*- and *trans*-tetramethylenedicarboxylic acids and dealt with the methods of preparation of ethyl butanetetracarboxylate which on hydrolysis leads to adipic acid. Trimethylsuccinic acids, the identification of which had been a subject of controversy, were characterised.

During the next ten years, Bone followed up the work in a characteristically exhaustive manner, publishing seven more papers in the *Transactions of the Chemical Society* along with his collaborators Sprankling and also

H. H. Henstock and J. J. Sudborough. The last of these papers appeared in the *Transactions of the Chemical Society* in 1904. These early escapades in organic chemistry no doubt provided him with experience which later he made use of in the study of the products of slow decomposition of hydrocarbons, and more particularly in the study of the constitution of coal.

Even during these researches in organic chemistry he was being drawn back towards his deeper interest, the chemistry of combustion. In 1894, and again in 1897, he is publishing with J. Cain and extending his first research to study the incomplete combustion of acetylene, mixtures of cyanogen and hydrogen and of pentane with oxygen. These investigations overthrew the dogma of the preferential burning of hydrogen in hydrocarbon flames. Considerable controversy, however, continued to rage round the question as to how hydrocarbons burnt, in which H. E. Armstrong took a prominent part. Bone, thinking that an explanation might be found in the formation of intermediate compounds, set out on a new line of inquiry into their slow combustion about which next to nothing was then known.

But about this time he was also taking up the cudgels to see whether hydrogen would combine with carbon directly at temperatures of over 1000° to give methane. Berthelot had obtained acetylene in the electric arc, but it was considered methane was decomposed at high temperatures into its elements. Bone's work which he was carrying out at this time with Jerdan suggested that a definite equilibrium existed between hydrogen, carbon, and methane at 1100° C. and that at the temperature of the arc, although acetylene was the main product, methane and some ethane were formed. The paper in the Chemical Society *Transactions* appeared in 1901 and was an extensive piece of experimental work involving the separation of methane and ethane by diffusion and well illustrates Bone's experimental ability. Later he resumed the attack on this problem partly to dispel criticism of the former work and partly to demolish what he rightly considered to be erroneous views about the production of acetylene such as those of Vivian Lewis. Eventually he and H. F. Coward showed that by passing hydrogen for a long period over 0·3 g. of pure carbon at 1100° C. it could be almost completely combined to form methane. He went to the trouble to get special lead-free Berlin procelain tubes, having found by analysis that those which purported to be lead-free contained traces of lead which were preventing the complete conversion of the carbon into methane.

In 1898 appears a note on gas analysis apparatus in the Chemical Society *Proceedings*. This was the forerunner of the well-known Bone and Wheeler apparatus and was a characteristic outcome of Bone's insistence on careful and accurate work. He was dissatisfied with existing methods and set himself to improve them on the lines of Frankland and MacLeod's methods. The design has been almost universally adopted, subsequent improvements having been incorporated.

It is interesting to note a short paper which Dixon published along with Bone on the analysis of natural gas at Heathfield, Sussex. Dixon did not bring Bone into his researches on detonation and this is the only paper that was published in their joint names. Bone, however, was destined later to greatly extend Dixon's work on detonation.

Bone's researches on the slow oxidation of hydrocarbons constitute his most significant early work: they mark the central feature of his life's work. The first paper of this series was published along with R. V. Wheeler in 1902 on the slow oxidation of methane. Methane and oxygen mixtures were heated in borosilicate glass bulbs for different lengths of time and the products were analysed. The products in turn were submitted to the same treatment and it was shown by a process of exclusion that the carbon oxides were derived from the oxidation of the methane and not by oxidation of the carbon monoxide or through the action of steam. This first paper contained no reference to the hydroxylation theory.

The second paper appearing in 1903 described a new method in which the gases were circulated round and round through a hot tube so that very much larger quantities of gas could be treated. This proved that the oxidation occurred *via* formaldehyde and left it a matter of conjecture whether a hydroxylated product, $CH_2(OH)_2$, was first formed, for no methyl alcohol had been found in the liquid products. On this occasion, Armstrong also published a paper setting forth his ideas about the oxidation of hydrocarbons and the importance of water acting as an electrolyte in the process. He revived the suggestions which he had made in 1874 that hydroxylation would occur step by step along with the formation of hydrogen peroxide. Shortly afterwards Bone and Stockings published the most exhaustive and characteristic of this whole series of papers. By the methods he had already employed for methane the products of the slow oxidation of ethane were studied. It was in this paper that he stated that " the combustion proceeds in several well-defined stages during which the oxygen enters into and is incorporated with the hydrocarbon molecule forming oxygenated intermediate products by successive stages of hydroxylation." They found no direct evidence of the production of ethyl alcohol (except when ozone was used) but showed that acetaldehyde and steam were the first products to be detected. They obtained hydrogen, methane and ethylene, but showed them to be secondary products arising from the acetaldehyde and formaldehyde produced. Investigations followed on the oxidation of ethylene and of acetylene to which the hydroxylation scheme was equally applicable. Although no vinyl alcohol was then isolated in the early stages of the ethylene oxidation, the isomer acetaldehyde was found to be formed. Strong evidence against some of Armstrong's views was adduced, particularly those relating to the intervention of water, which in a paper with G. Andrew was shown not to affect the oxidation of a hydrocarbon, although in agreement with H. B. Baker he found it to affect the combustion of hydrogen.

Bone's power as an investigator, his experimental ability, his literary talents, his thoroughness, his careful observation and attention to detail, and his use of the method of elimination of possibilities are strikingly

shown in these series of papers. Much of his subsequent work was a development of these important investigations, and during the last ten years of his career he supervised much work designed to test and extend the views at which he had arrived.

The long paper which he published with J. Drugman in 1906 on the explosive combustion of hydrocarbons was also very important. In it he extended the view that the initial encounter of the hydrocarbon and oxygen results in the production of an oxygenated molecule in flame combustion just as it does in slow combustion, the same hypothetical hydroxylated substances being formed as transient molecules. He isolated aldehydes from the interconal gases of the flame. Thermal decomposition, he agreed, played a more prominent part in the flame, but still not a dominant part, the oxidation being a much more rapid process than any dissociation of the hydrocarbon. He allowed that his former work with Lean, and later with J. C. Cain, though it did disprove the theory of the preferential combustion of hydrogen, did not disprove the theory of the preferential combustion of carbon. But he argued that these later experiments on the different products obtained from mixtures of ethane, ethylene, and acetylene respectively with oxygen having the same C : H : O ratio, made such a theory quite untenable. He held the view that the oxygen was attached to the hydrocarbon molecule forming first a monohydroxylate; but in the detonation of ethylene mixtures he considered that a dihydroxy-product might be formed by single impact with an oxygen molecule. At this stage of his work he seems to have come to the conclusion that his and Armstrong's views were practically identical except for the intervention of water and the consequent production of hydrogen peroxide. Most of this work was carried out at Manchester, and Bone was elected Fellow of the Royal Society in 1905.

In 1906 Bone transferred to Leeds to organize a department of Fuel Technology at the University; the Gas Industry endowed the Livesey Chair and Bone became the first Professor of Coal Gas and Fuel Industries. While at Leeds Bone extended his work on the mechanism of the combustion of hydrocarbons by studying explosions at pressures up to fifty atmospheres. These investigations, carried out from 1906 to 1912, were published in the *Philosophical Transactions* in 1915, after he had moved to South Kensington. His collaborators in this work were H. Davies, H. H. Gray, H. H. Henstock, and J. B. Dawson. The high-pressure apparatus was designed with the help of Petavel, whose well-known manometer was utilized for recording the rate of rise of pressure. The maximum pressure measured in this work was about 400 atmospheres.

It was concluded that an equimolecular mixture of methane and oxygen reacted as a single transaction through to the dihydroxy-compound which then produced formaldehyde and water, the formaldehyde providing CO and $H_2$; only with mixtures with more methane than the mixture $3CH_4 + 2O_2$ was there any appearance of carbon separation. The effect of successive increase in the hydrogen–methane ratio on the oxygen distribution showed that methane was burnt in preference to the hydrogen, and carbon monoxide was found more effective than hydrogen "in pulling away oxygen from the predominating affinity of the hydrocarbons." Similar experiments were carried out on ethylene and on ethane, and all the results strongly supported the views which had been put forward in the earlier papers on the combustion of hydrocarbons through successive stages of hydroxylation. Under certain conditions carbon separated and steam was formed and this was explained by decompostion of the vinyl alcohol first formed prior to dihydroxylation. In the case of ethane it was found that (1) a flame of long duration increased the amount of carbon formed, (2) conditions leading to rapid cooling gave more aldehydes and steam, and (3) the high temperature of a detonating explosion gave opportunity for the carbon to be attacked by the steam formed. Although hydrogen appeared to show much less affinity for oxygen than methane, yet the liberation of energy, as shown by the rate of rise of pressure, was much greater for hydrogen.

These interesting high-pressure studies were resumed when Bone was established in the new laboratory at South Kensington; and the results were published in a series of fifteen papers from 1921 to 1933. The first of these was on explosions in hydrogen–air and carbon monoxide–air mixtures. The papers had been written and a few final checks were being made, when an accident in the laboratory led to the death of A. W. Haward who was assisting Bone in this work. Although deeply affected by this untoward disaster, it was characteristic of Bone's courage to realize that what his collaborator would have most desired would be the uninterrupted prosecution of the work, and he set himself to carry on these high-pressure investigations with all the more pertinacity. He eventually succeeded in measuring explosion pressures of over 7000 atmospheres. It is only necessary to refer to Bone, Newitt, and Townend's book on "Gaseous Combustion at High Pressures" to realize how meticulously careful Bone was in all such high-pressure work and rules had to be implicitly obeyed.

Bone and Haward's investigations of the combustion of hydrogen–air and carbon monoxide–air mixtures showed that the rate of rise of pressure was much more rapid for hydrogen than for carbon monoxide. Not only the time to maximum pressure was delayed in the case of the latter, but also the rate of pressure fall after maximum pressure was diminished. Even 1 per cent. of hydrogen, however, in the carbon monoxide–air mixture counteracted these effects. Bone considered that hydrogen was burnt as a termolecular process, $2H_2 + O_2 \longrightarrow 2H_2O$, but that carbon monoxide combines with oxygen atoms: when hydrogen is present, the burning of the carbon monoxide is assisted by the reaction $CO + H_2O = CO_2 + H_2$. The anomalies connected with the combustion of carbon monoxide, thus found, led him to a very exhaustive attack on the effect of pressure on its combustion.

The rest of the high-pressure work was carried out along with his assistants, D. M. Newitt and D. T. A. Townend. A remarkable effect of nitrogen on the combustion of carbon monoxide was found. Taking

mixtures of carbon monoxide with $mO_2$ and $nH_2$ where $m + n = 4$, it was found that nitrogen greatly increased the time to maximum pressure, lowered the maximum pressure, and retarded the rate of cooling. The results previously found with carbon monoxide–air mixtures were thus accounted for by this specific effect of nitrogen, which was not shown by argon, or by excess of carbon monoxide, and was prevented by a small quantity of hydrogen. It was supposed that the nitrogen absorbed vibrational energy by resonance from the carbon monoxide and that the energy was only slowly given out in the cooling period. It was found that although nitrogen oxides were produced in much greater profusion in carbon monoxide explosions than in hydrogen explosions, these resulted as a secondary effect, and did not account for the delaying action of the nitrogen. The nitrogen was first activated in some way by the carbon monoxide, and then part of the activated gas was oxidised to nitric oxide. The effect was only noticeable at pressures higher than 10 atmospheres' initial pressure.

Observations were then extended to higher initial pressures (175 atms.) in order to study the effect of dissociation, which could be suppressed by excess of carbon monoxide. Results in carbon monoxide–oxygen mixtures with an excess of 4 mols. of CO were compared with mixtures with an excess of 4 mols. of oxygen, and it was concluded that neither dissociation nor nitric oxide formation accounted for the effect of nitrogen, which appeared to depend on the absorption of radiation. Further experiments with helium confirmed the observations with argon and provided experimental data for the determination by D. M. Newitt of the volumetric heats of $CO_2$ and steam. Using a bomb one metre long, with quartz windows, it was shown that emission in the ultra-violet was less when excess nitrogen displaced excess oxygen and that the nitrogen peroxide absorption bands were only visible in the products after the gases had cooled down; the formation of the nitric oxide was not found to occur till after all the radiation in the flame which affected the spectrum plate had been emitted. These results appeared to confirm the previous conclusions.

Partly in order further to investigate the effect of pressure on the delaying action of nitrogen and partly to determine the effect of pressure on the production of nitrogen oxides, experiments were carried out at still higher pressures. With the financial assistance of Imperial Chemical Industries and the advice of Sir George Hadcock, F.R.S., a bomb capable of withstanding 10,000 atmospheres was constructed. Explosions were carried out at maximum initial pressures up to 750 atmospheres in the case of hydrogen–air and 1000 atmospheres in the case of carbon monoxide–air, reaching maximum pressures as high as 7000 atmospheres. The delaying effect of nitrogen was a maximum at 150 atmospheres initial pressure, and did not increase above this pressure.

With the rapid cooling on expansion of the explosion products obtained by the aid of bursting disks, it was found that as much as 5·4 per cent. of nitric oxide could be obtained 0·06 second after the pressure maximum with mixtures containing $3O_2 + 2N_2$ at 70 atmospheres' initial pressure. This was more than twice that obtainable in the products without the use of the bursting disk. Experiments were also made by continuously burning carbon monoxide and 50 per cent. $O_2/N_2$ in a pressure vessel at 100 atmospheres, but under these conditions not more than 2 per cent. of nitric oxide was obtained in the exist gas. Other experiments in the high-pressure vessels were made on the behaviour of hydrogen and steam in suppressing the effect of nitrogen. Measurements had not been made during Haward's work with less than 1 per cent. of hydrogen; it was found, however, that the effect of hydrogen only commenced at 0·65 per cent.; quantities greater than this appeared to alter the character of the explosion and cause a kind of " knock." Hydrogen appeared to be more effective than steam.

The main impression made in reading the account of these researches is the thoroughness with which these difficult and elaborate experiments were carried out. They reflect Bone's tenacity of purpose; no difficulty was too great that it could not be surmounted and work was carried to the limit of the possibilities of the experimental methods he had chosen. They reflect, too, his ability in choosing assistants capable of carrying out his programme.

These high-pressure investigations led on to his work on the combustion of carbon monoxide. He was determined to discover whether it could be burnt without the intervention of steam. Dixon in 1880 had found that careful drying of carbon monoxide–oxygen mixtures prevented combustion. Armstrong had persisted that water, an " electrolyte," was necessary. Bone gives a full account of the history of the problem in his paper with F. R. Weston (*Proc. Roy. Soc.*, 1926, **110**, 615).

Bone first set himself to settle whether water is necessary for the combustion of carbon monoxide at ordinary pressure and then to find out the effect of increasing the pressure. The results were that after drying carbon monoxide–oxygen mixtures with the utmost " Bakerian " precautions and leaving them to dry over pure $P_2O_5$ for six months or even longer the mixture would ignite and propagate flame, provided the energy of the igniting spark was sufficient. The bulbs were fired, photographed and the combustion witnessed by H. E. Armstrong, A. Smithells, Sir R. Robertson, and H. B. Baker.

Still not satisfied, Bone then made further tests. He was determined to remove all suspicion that there might be any water present in the gas mixture or in the electrodes at the time of firing. They were rigidly dried to a limit, employing an " elaborate ritual "; this time the drying period was 1000 days. The bulbs were fired in the presence of H. B. Dixon and W. E. Garner.

The second part of the work related to pressure experiments. The apparatus was dried by heating and circulating nitrogen for periods of weeks, and the gases were dried for periods of a year. It was found that with the relatively weak energy of the spark employed, ignition did not occur below 2 atmospheres, that at 2·75 to 5 atmospheres it took place with difficulty, but that at 10 atmospheres ignition occurred every time.

Spectroscopic observations carried out by his assistants Newitt and Weston showed that the steam lines, which were prominent in the indirect combustion of carbon monoxide in the presence of water or hydrogen, were replaced by the continuous and banded spectra characteristic of the direct combustion when the mixtures were dried. As the pressure increased the latter spectrum predominated even when hydrogen was present. The emission range in the ultra-violet was reduced when nitrogen was present at high pressures. In 1934 further spectroscopic observations were published. Carbon monoxide was burnt in oxygen in a special bomb, provided with windows, up to pressures of 100 atmospheres, and it was found that the steam lines were suppressed at pressures higher than 30 atmospheres.

By this very elaborate and characteristically pertinacious piece of experimental work, Bone established that carbon monoxide can burn without the intervention of steam, and that as the pressure is increased above 10 atmospheres the direct method is favoured. A man of less energy and obstinate power of will might have drawn such conclusions from a few special experiments, but there would have still been doubts; Bone determined to remove all doubt, however much trouble it entailed.

Bone commenced researches in 1903 on the catalytic combustion of hydrogen and carbon monoxide along with R. V. Wheeler, G. W. Andrew, and H. Hartley at temperatures well below their ignition temperatures. Employing a variety of typical surfaces, he and his associates were led to conclude (i) that the power of accelerating gaseous combustion was possessed in varying degrees by surfaces, basic, acidic and metallic; (ii) that the accelerated surface combustion was dependent on a prior occlusion of the combustible gas and probably also of oxygen; (iii) that the rate of the absorption determines the rate of the reaction and therefore the latter is dependent on the pressure of the combustible gas. Bone disagreed with Bodenstein's conclusion that with platinum oxygen absorption alone determined the rate of the reaction, for he found that prior treatment with the combustible gas greatly accelerated the rate of combustion at the surface. He also showed that his results were inconsistent with the alternate reduction and oxidation hypothesis. By this work, Bone claimed to have anticipated in a general way the views of Langmuir that such catalytic reactions are preceded by activated adsorption at the surface of the catalyst, and in his lecture given before the Society of Chemical Industry he quotes the following sentence from a private communication from Langmuir, " the general view point which you had in 1906 was much ahead of others of that time, and is in many ways closely related to that which I have developed independently from a rather different experimental basis."

Bone published a further series of papers on catalytic combustion (1925—27) in the *Proceedings*, more particularly relating to the catalysis of carbon monoxide–oxygen mixtures in contact with gold, with nickel and copper and their oxides, and with a fireclay surface. He pointed out that " the dominant factors in one set of circumstances may be demonstrably different from those prevailing in another," and his experiments led him to somewhat different conclusions from those come to by Langmuir and others who worked at much lower pressures and higher temperatures. He concluded that the activated adsorption was not confined to the surface layers, and that both the carbon monoxide and the oxygen had to be adsorbed for the reaction $2CO + O_2 \longrightarrow 2CO_2$ to occur at these lower temperatures. In the case of the oxide surfaces no reduction of oxide to metal occurred but merely the formation of oxygen–metal–CO complexes on the surface. The action at the fireclay surface depended on the pressure of the complete combustion mixture ($2CO + O_2$) and on the carbon monoxide pressure for other mixtures.

In some very careful work on the effect of moisture on the catalytic activity of such surfaces, it was found that drying caused a temporary increase in activity by removal of the film of water which " lags " the surface. Prolonged drying, however, ultimately altogether stopped the catalysis at the silver and gold surfaces whose activity could be re-established on introducing moisture; in the case of fireclay the loss of activity could not be so restored.

This summarises in a few words the main results of Bone's extensive work on catalytic combustion. It has been carried on and extended in other directions by G. I. Finch, F.R.S. Bone was impatient of half-developed theories. In that same lecture he remarked " while much remains to be done in the way of classifying the subject of catalytic combustion by further experiments, let us beware of the creeping in of mystical notions that will blur and distort our vision. For when one hears not only of supposed ' deactivation ' on the hot walls of containing vessels, but also of ' reaction-chains ' executing Brownian movements thereon, one wonders whether, were Vernon Harcourt to come to life again, he would not be incited into breaking heads against laboratory walls." Bone looked at things in a large macroscopic way; he took a dislike to the microscopic behaviour of things.

In conjunction with C. D. McCourt, Bone developed (1908—12) the " incandescent " surface combustion process whereby an explosive mixture of gas and air in proper proportion for combustion, or with slight excess of oxygen, was caused to burn without flame in contact with a granular incandescent solid. The process was adapted to crucible and muffle furnaces, to steam raising in multitubular boilers and to " radiophragm " heating for cooking and other purposes. For six years two large gas-fired surface combustion boilers were run on coke oven gas at Skinningrove Iron Works with a thermal efficiency of 92·7 per cent. of the net calorific value of the gas. In this connexion he was asked to lecture in other lands. Quoting from the lecture already referred to, he best tells his own story :

" I received in August 1911 a cabled invitation to expound and demonstrate the process experimentally at the Annual Congress of the American Gas Institute at St. Louis on October 19th of that year, all expenses of myself and two assistants to be paid by our hosts. Accordingly, we took out nearly a ton of apparatus, and

duly lectured and demonstrated to an enthusiastic audience for upward of three hours on the afternoon in question, the longest infliction I have ever perpetrated. Immediately afterwards we were banqueted for some hours with topical musical and pictorial interludes in real Western style; and, on my rising to respond to the toast of my health, the band struck up ' The Man that Broke the Bank at Monte Carlo.' On my inquiring what it meant, it was explained that the expenses of our show had literally cleaned out the American Gas Institute, who had perforce to send the hat round their industry to meet them, and that it was a tribute to a professorial Bone that had skinned them so easily.

" I repeated the lecture twice in New York and also at the Franklin Institute in Philadelphia, and was overwhelmed with the generous hospitality which Americans always extend to their guests; unfortunately, I also contracted severe ptomaine poisoning, and returned home a physical wreck. A year later I had the honour of lecturing on the subject before the Deutsche Chemische Gesellschaft in Berlin and the pleasure of meeting F. Haber, Jacobsen, Otto Witt, Will, and other distinguished chemists, whose appreciative kindness remained a pleasant memory during the dark days of the Great War which broke out so soon afterwards."

From 1930 to 1937 Bone published a further series of six papers along with various collaborators on the slow combustion of hydrocarbons (methane, ethane, ethylene and acetylene). The method employed in most of this new work was to heat the gaseous mixture in a silica bulb, measuring the length of the induction period and rate of reaction by the pressure change. The final products, gaseous and liquid, were analysed, deriving therefrom an accurate measure of the distribution of carbon amongst the products to balance with the carbon in the hydrocarbon, or by cooling the reaction vessels down rapidly a precise knowledge of the main products formed at various stages of the reaction could also be obtained. The most reactive mixtures were found to be those which would give rise directly to alcohols; the induction periods and reaction times were shortened by aldehydes and by alcohols. Peroxides were not found except in those stages of reaction in which most aldehyde is obtained. Large amounts of alcohols were found by Newitt and Bloch to be formed in the pressure oxidation of methane and ethane.

In 1927, as a result of investigation of the phenomenon of " knock " in internal combustion engines, views had been expressed that the combustion of hydrocarbons was autocatalytic (Egerton and Gates) and that peroxides were first formed (Callendar and Mardles). There followed much other work, for instance, the combustion of ethylene (Hinshelwood and Thompson), the combustion of butane, etc. (Pease), all of which indicated that the hydroxylation theory was an incomplete explanation of the process of combustion of a hydrocarbon, and that it was necessary to introduce the chain reaction mechanism first applied to the combustion of phosphorus by Semenov. Bone fought for the sufficiency of the hydroxylation theory and defended it not only on the grounds that the opponents had not provided definite positive evidence of the formation of peroxides, but also he supported it by a wealth of careful experiment.

Suffice it to write here that Bone was retentive of the ideas he had already formulated and was slow to modify them because he rightly refused to put forward any modification until he was convinced of the basis of the new facts or had satisfied himself by experiment that such was necessary. His last paper on " The slow combustion of methane, methyl alcohol, formaldehyde and formic acid," although it repeats that the hydroxylation theory " rests securely on a firm basis of unimpeachable analytical facts," concedes that " the slow oxidation is autocatalytic " and that the aldehydes formed are peroxidised to some extent. A considerable amount of misunderstanding arose owing to the hypotheses being applied to different classes of hydrocarbons. Bone did not examine the behaviour of higher hydrocarbons, and what may be true for methane is not necessarily so for butane.

The experiments carried out in these latter years are undoubtedly the most careful and complete experimental study which has yet been made on the slow combustion of the simpler hydrocarbons, and show that the hydroxylation scheme specifies the main products, though it does not formulate precisely how they are formed, in fact does not tell the whole story. Bone gave a summary of his views and the evidence on which they were based in the Bakerian Lecture (1932), and a year later in a lecture to the Chemical Society. These papers show the power Bone possessed of marshalling a bold array of experimental evidence.

Perhaps the most striking section of Bone's later work was that which he carried out on Flame Propagation with the help of R. P. Fraser. Bone soon recognised and in every way encouraged the development of Fraser's special talents for photography. While in the course of studying detonation in gaseous mixtures, W. Payman and R. V. Wheeler published a generalisation about flame speeds in different blends of limit mixtures which Bone considered was untenable, and he set out to demolish it with characteristic thoroughness. In the course of this work many anomalies were discovered, such as propagation of flame at different speeds in the same mixture. Some beautiful photographs were obtained of methane–oxygen mixtures burning in closed and open tubes showing the streamers of burning particles from the spark and the burst of luminosity as compression waves pass back and forth through the burnt products. Amongst other matters studied were the effect of ethylene on the combustion of electrolytic gas first noted by Sir Humphrey Davy, similar effects of acetylene, the influence of electrical and magnetic fields on the propagation of flame, the determination of the conditions for maximum speed of a flame in carbon monoxide–oxygen mixtures and the effect of moisture thereon. These flame investigations culminated in three papers in the *Philosophical Transactions* (1929, 1931, and 1936) in which are collected the most beautiful examples of flame photography which have been achieved.

The progressive drying of a carbon monoxide–oxygen mixture was found to greatly lower the flame velocity, but this hindering effect could be overcome by imposing a strong electric field on the medium. It was shown

that under the influence of successive superimposed shock waves, the speed at which flame starts may be raised in successive abrupt stages each one giving rise to a new uniform flame speed, until the speed nearly approaches that of the shock wave itself. If the region in front of an advancing flame is under the influence of shock waves detonation might be set up ahead of the advancing flame, and in confirmation of the observations of C. Campbell and D. W. Woodhead the detonation flame photograph may possess a banded appearance, due to the head of detonation travelling in a helical path through the tube. This latter phenomenon was studied in great detail by means of a camera for very high-speed flame photography consisting of a stainless steel mirror rotating in a vacuum up to speeds of 30,000 r.p.m. As Bone remarks in a Royal Institution Lecture (1933) : " It is indeed a wonderful instrument and our only regret is that Dixon did not live to see it." Bone and Fraser examined the effect of electric fields on detonation flames, which were found to reduce the speed or even to cause detonation to cease when orientated so as to draw out electrons from the flame front.

They sum up their conclusions as follows :

" A new view of the detonation-wave in gaseous explosions is advanced. For it can no longer be regarded as simply a homogeneous ' shock wave,' in which an abrupt change in pressure in the vicinity of the wave-front is maintained by the adiabatic combustion of the explosive medium through which it is propagated; but it must now be viewed as a more or less stable association, or coalescence, of two separate and separable components, namely of an intensively radiating flame-front with an invisible shock wave immediately ahead of it; and whether persistent ' spin ' is developed or not depends upon the stability or otherwise of their association.

" According to the new view, detonation in an explosive gaseous medium is the propagation through it, as a wave, of a condition of intensive combustion, initiated and maintained in a shock wave by radiation from an associated flame-front; and that ' spin ' ensues whenever the conditions are such that the radiation from an attenuated flame-front causes a localised intensive excitation of molecules in the ' shock wave ' just ahead of it. The resulting ' head ' of detonation, in which an intensive combustion is thus localised, then begins to rotate in the medium, eventually pursuing a spiral track along the tube quite close to its walls. There is, however, no rotation of the medium as a whole, but only of such a ' head,' or perhaps ' heads,' of detonation."

These final investigations on the detonation flame are a fitting conclusion to the work on combustion of one who described himself as " ever a fire worshipper."

Bone and Townend were the authors of a very welcome book on " Flame and Combustion," published in 1927.

Bone's influence on the study of coal and fuel economy in general has been widespread. His book, " Coal and its Scientific Uses," published in 1918, drew attention to the importance of studying coal as a chemical substance. This book was followed in 1936 by a more comprehensive treatise : " Coal, Its Constitution and Uses," written in collaboration with G. W. Himus.

Bone often pointed out that the subject of a chemical survey of our British coal seams originated with the British Association Fuel Economy Committee, of which he was Chairman (1915—22), and that the Fuel Research Board itself was an outcome of that Committee's successful pioneering work; other influences no doubt shared in the birth both of the Board and of the Survey for which it is responsible. He was a consultant to the Board from its inception in 1917 to 1930.

In 1919 Bone started his researches on the constitution of coal. In common with many other workers, he selected pyridine for his first experiments on the extraction of the constituents, but abandoned its use at an early stage, largely owing to its toxicity. The bulk of his work on extraction was carried out with benzene under pressure, although his experiments with other solvents showed that resins could be isolated from coal in a pure state. A method for Soxhlet extraction of coals with benzene under pressure was evolved and applied to a large variety of coals. The extracted material (up to 15 per cent. of the coal substance) was resolved into four fractions: I, soluble in light petroleum; II, insoluble in light petroleum; III, soluble in ethyl alcohol; and IV, insoluble in ethyl alcohol. Fractions I and II were soluble and fractions III and IV insoluble in a mixture of light petroleum and benzene. It was found that the coking propensities of the coal were dependent on the contents of fractions III and IV, which fractions were replaced by phenolic bodies in brown coals and lignites. The residue after extraction of a coking coal was found to be completely non-caking on carbonisation, except when mixed with fractions III and IV obtained from a coking coal.

Bone also devised the standard " Bone and Silver " method for the determination of the total volatile matter in coal. He carried out experiments on the carbonisation of brown coals and lignites at temperatures below 800° C. as a possible method of enhancing their fuel values. He suggested that these coals could be considerably " up-graded " by suitable heat treatment, as a result of which the Bone–Wood fuel improver was devised. In 1926 Bone began work on the oxidation of coal and the residues from benzene–pressure extraction, by means of boiling alkaline permanganate. A method was standardised and applied to a large selection of coals representative of many geological and geographical formations. From the products of oxidation all the benzenecarboxylic acids, with the exception of benzoic acid, were isolated. Quantitative oxidations demonstrated the essential benzenoid structure of the main coal substance, with progressive development of the benzenoid character as maturity of the coal increased. The essential chemical identity between " dull " and " bright " coals was also shown.

In order to obtain more precise knowledge of the mechanism of alkaline permanganate oxidation under these standardised conditions, an extensive investigation was undertaken of the behaviour of a number of

organic substances of known constitution when subjected to treatment identical with that which had been previously applied to coals. It was found, *inter alia*, that this method of attack was purely degradative and that no product of oxidation was more complex than the starting material. This communication to the *Proceedings of the Royal Society* early in 1938 was Bone's last published work.

Bone had maintained, from his earliest days, a very close connexion with the Iron and Steel Industry, so it is fitting to conclude the account of his scientific activities by reference to his work for that industry which he was still busily engaged upon up to the time of his death. While at Leeds he made a valuable study of the gas producer and of the reactions going on in the fuel bed and their variation with depth, and later at the Imperial College he commenced an exhaustive laboratory study of the reactions in the Blast Furnace which is still being prosecuted by his collaborator, Dr. H. L. Saunders. The fundamental information so obtained is of great use to the Industry.

The equilibrium in the system—oxides of iron, oxides of carbon—between 380° and 1200° C., was studied and this led to the investigation of the catalytic decomposition of carbon monoxide at 450° C. and the influence of the carbon so produced on the reduction of the ore. This carbon formation, so long as it is confined to the surface of the ore, has a disintegrating action upon the ore and hastens reduction, but accumulation of the carbon is detrimental. The reduction at 750° by the carbon impregnating the ore was found to be more rapid than the direct reduction by the blast furnace gas. Measurements of rate of reduction of oxides of iron by blast furnace gas and the effect of small additions of steam and hydrogen thereon were made over a temperature range 450—1000° C. when the variables were (1) the $CO_2$ content in the reacting gases, (2) the time of contact between the gases and the ore, and (3) the velocity of the gas at the ore surface. Hydrogen was found to be more effective in reduction than the equivalent carbon monoxide at high temperature, and it also accelerated the carbon deposition reaction.

These laboratory investigations have been supplemented by a study of the composition of the gases and state of the reduction of the ore in the interior of a blast furnace in actual operation, showing the great importance of the proper distribution of the burden.

Bone held very decided views on economic matters; his free trade convictions were brought to bear on the problems of the British Iron and Steel Industry, and in a paper published in *Chemistry and Industry* in 1932, in the middle of the slump, he boldly advocated " the erection of three or four large modern plants with coke ovens, blast furnaces, steel works and rolling mills co-ordinated so as to ensure the greatest fuel economy and placed under scientific management " and suggests that this step would be a more effective help than any " tariff protection," because " the production of the iron and steel to meet the world's demands is fast becoming an international question of the first magnitude in which all the chief producing countries are equally concerned."

In 1931 Bone received the Melchett Medal of the Institute of Fuel and delivered the Melchett Lecture with the title " A Century of Fuel Economy." He unfolded in a masterly manner the progress of fuel economy in the manufacture of iron and steel, in the manufacture of coke and gas, and in power production through the century: " It began and ended," he said, " amid the depression and dislocation of the aftermath of a great war; but in science was the key of Promise which unlocked the gates of Doubting Castle and delivered its prisoners from Giant Despair and it will do so again for us."

Bone was honoured by the award of the Davy Medal of the Royal Society in 1936.

Taking Bone's scientific activities as a whole, in accordance with the true spirit of experimental investigation, by new discovery he left more to explain than he explained.

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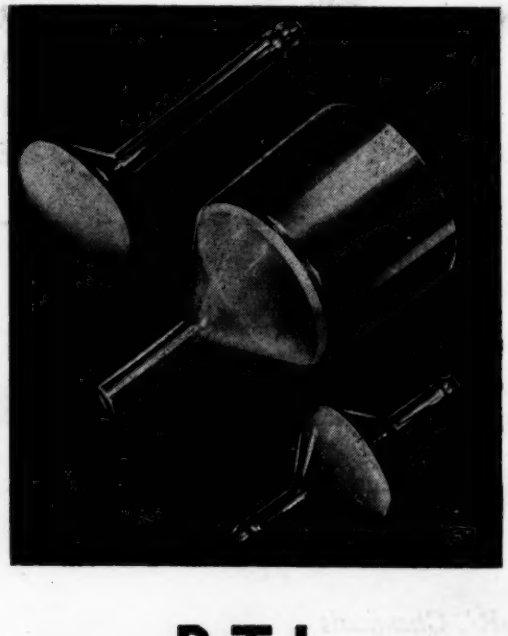

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